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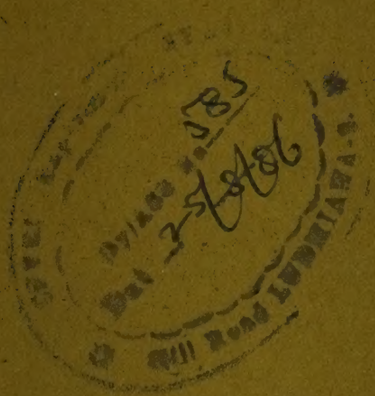

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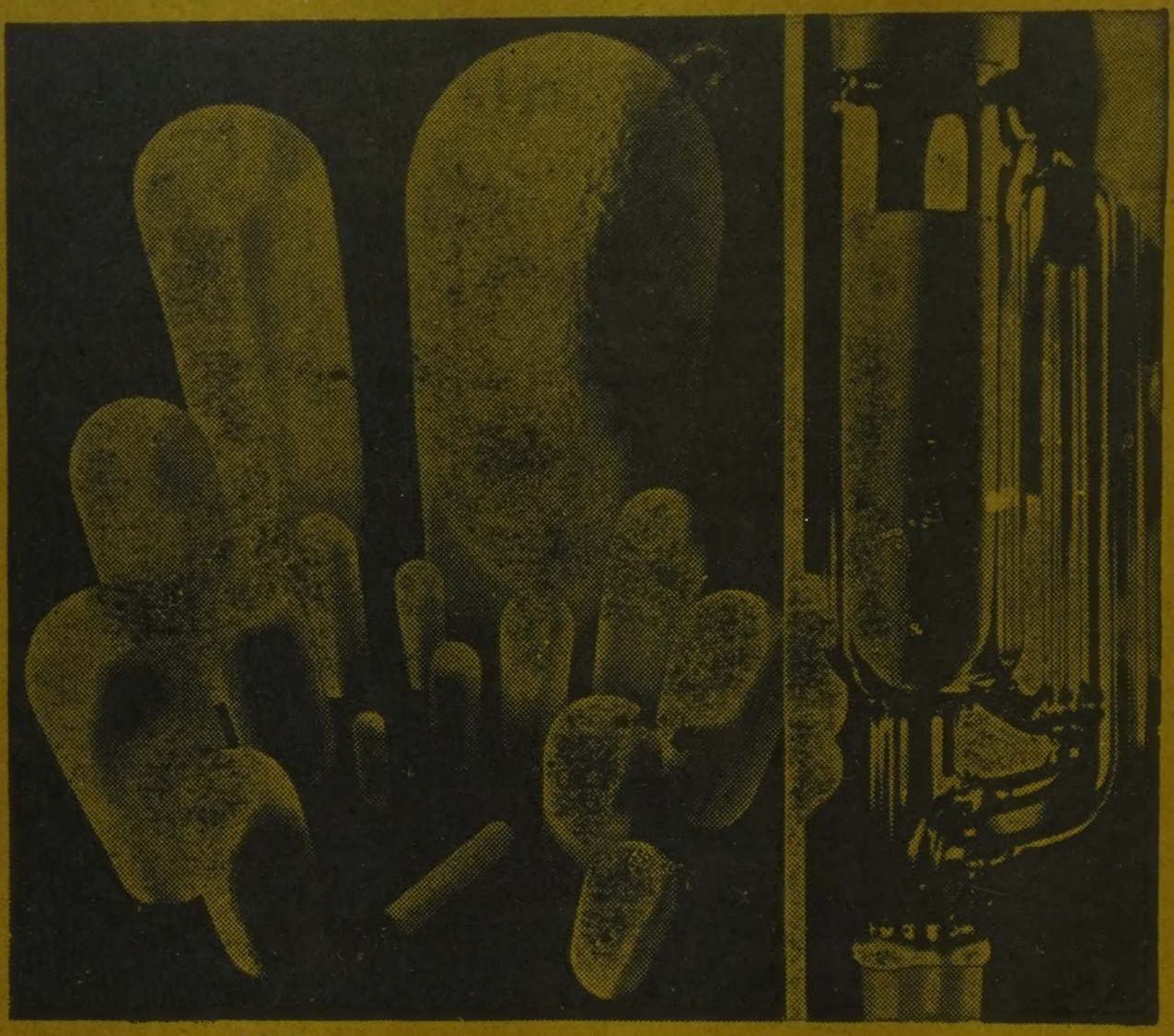

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Indian Journal of Chemistry

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Indian Journal of Chemistry
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A New Synthesis of 8-(ω-Carbomethoxyhexyl)-11-hydroxycyclopent-8(12)-ene-9-one, a Versatile Prostaglandin Intermediate

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Department of Chemistry, Indian Institute of Technology, Bombay 400 076

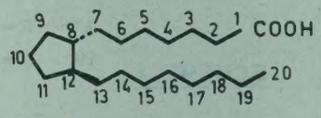
Received 16 *December* 1985; *accepted* 24 *January* 1986

8-(ω-Carbomethoxyhexyl)-11-hydroxycyclopent-8(12)-ene-9-one (V), a versatile prostaglandin synthon, has been synthesised starting from easily accessible undecylenic acid (VI). The synthesis involves preparation of dihydroxy undecanoic acid (IX) and its methyl ester (X), methyl 9-formylnonanoate (XI), the monoester (XII) and the corresponding unsaturated acid (XIII), γ-lactone (XIV), cyclopentenone acid (XV) and finally the all important PG-intermediate 2-(ω-carbomethoxyhexyl)cyclopentenone (IV). Its reduction with sodium borohydride gives the saturated alcohol (XVI), which via oxidation with Jones' reagent and bromination-dehydrobromination sequence could be converted back to IV. However, IV, on reduction with aluminium isopropoxide gives the allylic alcohol (XXIII), which is converted via acetylation into the acetate (XXIV). Subsequent oxidation of acetate (XXIV) with *t*-butyl chromate yields the keto-acetate (XXV), which on reduction with aluminium isopropoxide furnishes the hydroxy acetates (XXXII). The hydroxyl group in XXXII is protected as tetrahydropyranyloxy derivative (XXXIII). Hydrolysis of XXXIII with alkali leads to the hydroxy acids (XXXIV). Oxidation of XXXIV with Jones' reagent at low temperature for a short period yields the keto-acid (XXXV), which is esterified to give the ester (XXXVI). Finally, removal of the pyranyloxy group from XXXVI furnishes the versatile synthon (V), identical with the sample prepared by a known procedure.

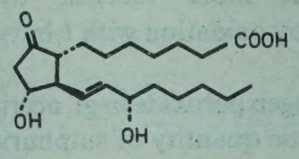
Prostaglandins (PGs), which are associated with most of the mammalian tissues and tissue secretions, are perhaps the most physiologically active compounds known so far. The system containing the fundamental framework has been named as prostanoic acid (I). Two typical examples from the PG-family are PGE_1 (II) and $PGF_{1\alpha}$ (III).

Synthesis of PGs and their analogues has attracted considerable attention during the last two decades and over 250 papers, covering various approaches for the synthesis of PGs have been published. As the PGs are chemically very sensitive and may have as many as five asymmetric centers [at C-8, C-9, C-11, C-12 and C-15 in case of $PGF_{1\alpha}$ (III)], their synthesis becomes a difficult exercise. Consequently, most of the existing syntheses are, perforce, complicated and attempts are constantly being made to develop simpler approaches for preparing this important class of compounds.

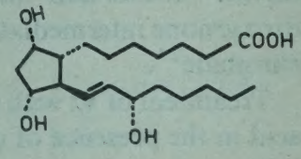
At the early stages, the cyclopentenone intermediate (IV) was used for the synthesis of the first pharmacologically active prostanoid by Bagli and Bogri[1]. Subsequently, many independent approaches were developed for the preparation of IV, which, in its turn, was converted into several other pharmacologically active prostanoids[2-8]. Subsequently, yet another versatile intermediate, the hydroxyenone (V), was prepared and successfully exploited for the synthesis of



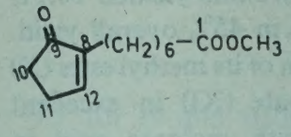
I – PROSTANOIC ACID



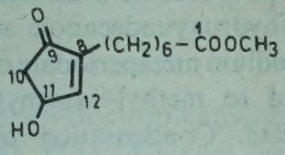
II – PGE_1



III – $PGF_{1\alpha}$



IV

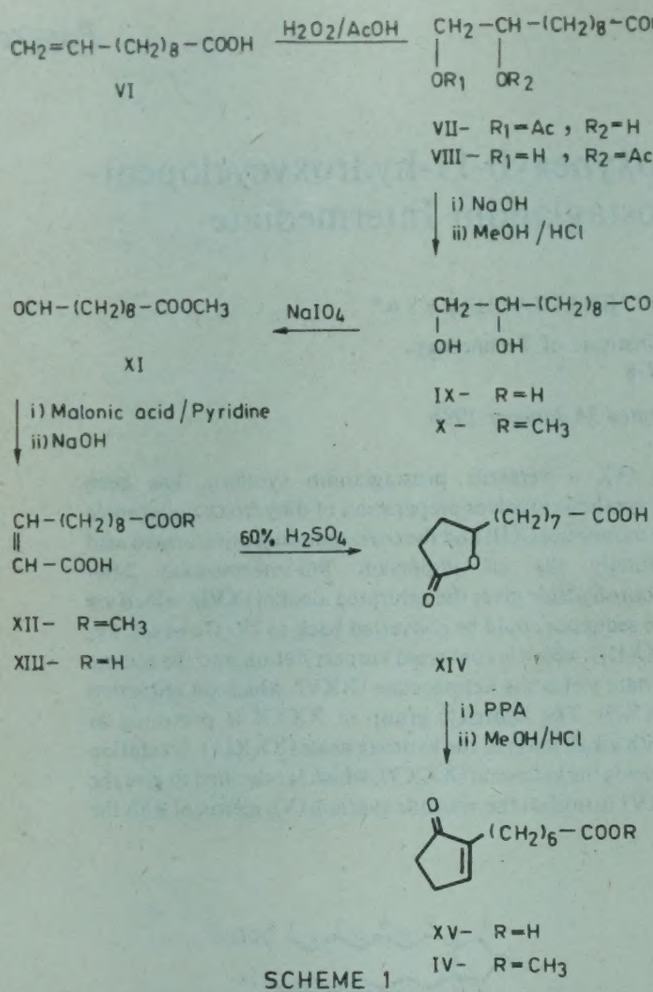


V

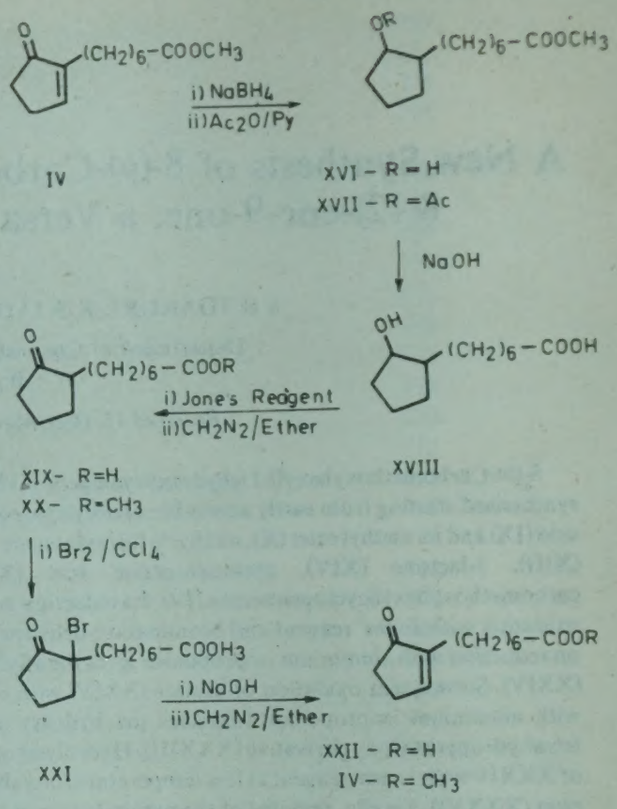
fully functionalised PGs. Today, four different routes are available for the synthesis of V, but leaving one, all the others involve microbiological or enzymatic mediation at some stage or the other[2,9,13].

Synthesis of PG-type compounds has been of interest to us for several years. Some of the results of our investigations in this direction[6,14-16] have already been published. We now report the experimental details of our previously documented[6] simple and economically attractive synthesis of the PG-intermediate (IV) from an easily accessible starting

†The paper forms parts of the Ph D theses of S B Thakur and K S Jadhav submitted to the IIT, Bombay, 1977.



SCHEME 1



SCHEME 2

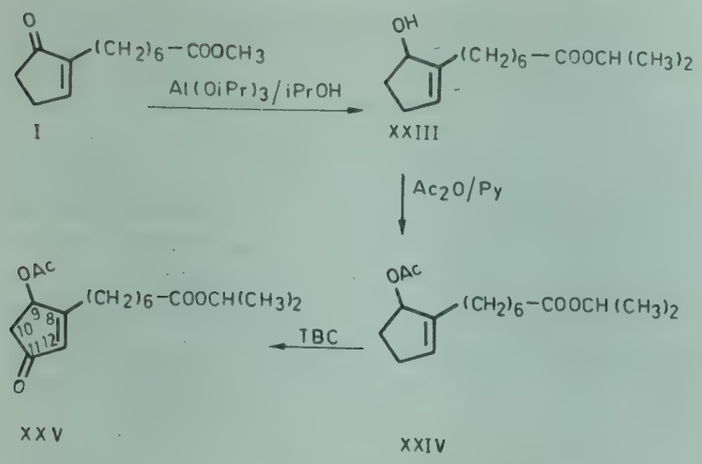
material, undecylenic acid (VI) (see Scheme 1), and its further conversion into the more versatile hydroxyenone intermediate (V) by oxidation with *t*-butyl chromate[14].

Treatment of VI with hydrogen peroxide in gl. acetic acid in the presence of catalytic quantity of sulphuric acid gave a mixture of isomeric hydroxyacetoxyundecanoic acids (VII+VIII). The mixture on saponification with sodium hydroxide yielded 10,11-dihydroxyundecanoic acid (IX) in 45% overall yield. Sodium metaperiodate oxidation of its methyl ester (X) led to methyl-9-formylnonanoate (XI) in excellent yield. Condensation of XI with malonic acid in pyridine solution resulted in the monoester (XII), which on saponification, afforded 2-dodecendioic acid (XIII). Treatment of XIII with 60% sulphuric acid at 130° gave the γ-lactone (XIV) in 55% yield, which on cyclodehydration using polyphosphoric acid gave the acid (XV) in 70% yield. Esterification of XV afforded the required PG-intermediate (IV).

We next focussed our attention towards the functionalization of C-11 in IV to obtain the more versatile PG-intermediate (V). Based on our earlier investigations[14] on allylic oxidation of various monoalkyl substituted cyclopentenes with *t*-butyl chromate, we thought of using the same reagent. For this purpose it was necessary to protect the existing carbonyl function at C-9 in IV before introducing the other at C-11, so that further manipulations would be possible. Our attempt of protecting it as the corresponding ethylene ketal was unsuccessful, because of, perhaps, conjugated nature of the carbonyl group in IV. In conjugated ketones it has been observed that the double bond shifts[17-19] out of conjugation during ketal formation, and the ketal formed is susceptible to even mild acid hydrolysis.

Sodium borohydride generally reduces a conjugated ketone to the corresponding allylic alcohol but in the case of enone (IV) (Scheme 2) it was observed to give the saturated alcohol (XVI). This conclusion was based on the fact that the acetate (XVII) (Ac_2O/Py) of XVI did not show in its PMR spectrum any signal for the vinyl proton in the region of δ 4.5 to 8. This was further confirmed by chemical evidence, as XVIII obtained by the hydrolysis of the acetate (XVII), gave the keto-acid (XIX) which on esterification with diazomethane yielded the keto ester (XX). Both XIX and XX were found to be cyclopentanone derivatives (IR, UV), confirming that the parent alcohol (XVI) was a saturated alcohol and not the expected allylic alcohol. However, the starting enone (IV) could be regenerated through a sequence of bromination, dehydrobromination and esterification reactions (XIX→XXI →XXII→IV) on the keto-acid (XIX).

Alternatively, the synthon (IV) was reduced with aluminium isopropoxide (Scheme 3), to yield the allylic



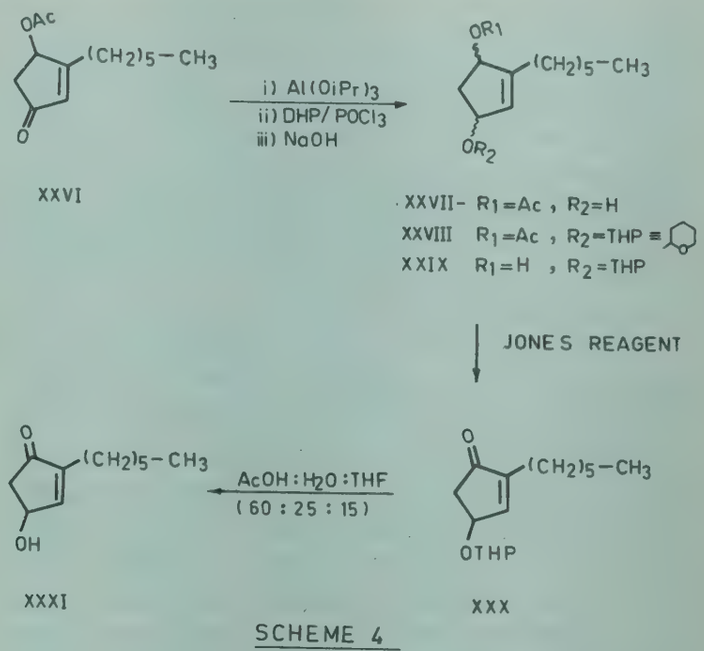
SCHEME 3

alcohol (XXIII) as the corresponding isopropyl ester in 93% yield. It was acetylated (Ac_2O/Py) to the allylic acetate (XXIV). Such a type of ester exchange during aluminium isopropoxide reduction, though not very common, has sporadically been reported in the literature[11].

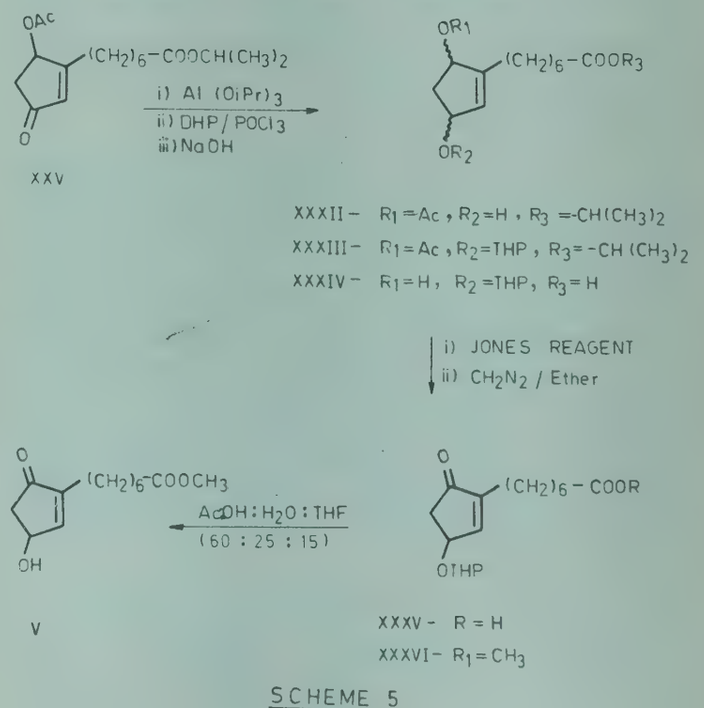
The acetoxy compound (XXIV) on being subjected to allylic oxidation with 2.5 mol per cent of *t*-butyl chromate in carbon tetrachloride at 80° for 20 hr, gave a mixture of products from which pure keto-acetate (XXV) was isolated by silica gel chromatography in 35% yield.

In order to obtain the required hydroxyenone (V) from XXV, it was necessary to interchange the oxidation states of the oxygen functions at C-9 and C-11 in XXV. It was thought that the reduction of C-11 carbonyl function and protection of the resulting alcohol as its tetrahydropyranyloxy ether would give ample opportunity to selectively hydrolyse the C-9 acetoxy function to yield 9-hydroxy-11-tetrahydropyranyloxy compound, which on oxidation followed by hydrolysis of the protecting group would give V. This approach looked highly prospective. However, as a precautionary measure it was tested first on a simple and easily accessible model compound (XXVI) which was obtained by the *t*-butyl chromate oxidation of dihydroisojasmol acetate[14].

Synthetic sequence employed for this purpose is outlined in Scheme 4. Thus, the keto-acetate (XXVI) was reduced with aluminium isopropoxide in the usual way to obtain the hydroxy acetate (XXVII), as a mixture of two geometrical isomers. This mixture was treated with dihydropyran in benzene in the presence of a drop of phosphorus oxychloride to yield a mixture of two isomeric tetrahydropyranyloxy-acetoxy compounds (XXVIII). Hydrolysis of this mixture with excess of 2% sodium hydroxide yielded the mixture of two isomeric hydroxy-tetrahydropyranyloxy compounds (XXIX). Oxidation of this mixture with equivalent quantity of the Jones' reagent in acetone at



SCHEME 4



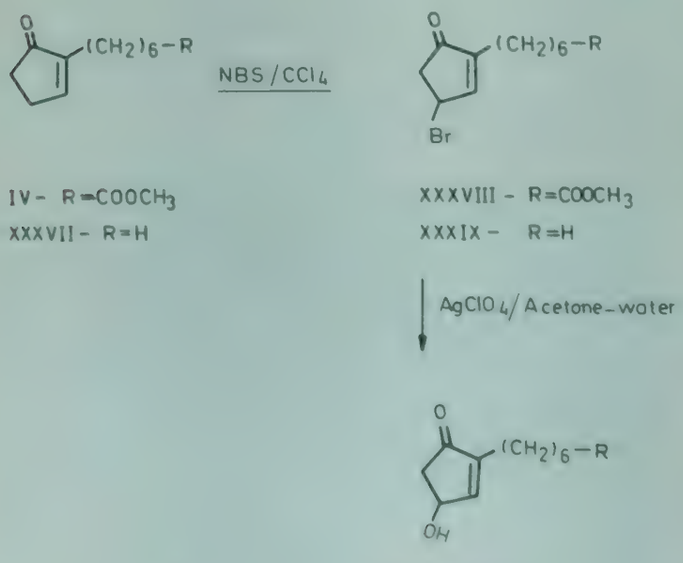
SCHEME 5

−10° for 10 min afforded the tetrahydropyranyloxy enone (XXX). The compound, thus obtained, was homogeneous (TLC) as the geometrical isomerism was lost because of the removal of the optical centre at C-9. The enone (XXX) was stirred at room temperature for 10 hr with a mixture of acetic acid-water-tetrahydrofuran (60:25:15) to yield the hydroxy-enone (XXXI).

After having successfully converted the model keto-acetate (XXVI) into the hydroxyenone (XXXI), the same sequence of reactions was employed on the compound (XXV) to obtain the required hydroxyenone (V) (Scheme 5). Thus, the keto-acetate (XXV) was reduced with aluminium isopropoxide to yield the mixture of two isomeric hydroxy acetates (XXXII). It is interesting to note that the reduction was

completed during 6 hr, as compared to the period of 20 hr required for the similar reduction of IV. This marked difference in the reactivity could be attributed to the steric factors. The steric hindrance towards the approach of the comparatively bulky reagent, like aluminium isopropoxide, is considerably more in the case of α-substituted ketones, such as IV, as compared to that in β-substituted ketone (XXV). The mixture of hydroxy acetates (XXXII) was converted into the corresponding mixture of tetrahydropyranyloxy-acetoxy compounds (XXXIII), which on hydrolysis with excess of 4% sodium hydroxide in aqueous methanol yielded the isomeric mixture of tetrahydro-pyranyloxy-hydroxy acids (XXXIV). It was then oxidized with Jones' reagent at $-10°$ for 5 min to obtain the keto-acid (XXXV), which on esterification with diazomethane yielded the tetrahydro-pyranyloxyenone (XXXVI). This ether was finally hydrolysed with acetic acid-water-tetrahydrofuran (60:25:15) for 10 hr to furnish the hydroxy-enone (V). Chemical and spectral characteristics observed for this compound were in excellent agreement with those reported in the literature[2,11,12].

For the sake of direct comparison of the hydroxyenone (V) and XXXI, the authentic samples of these compounds were prepared by an independent known procedure (Scheme 6)[10]. Thus, the enone (IV) and dihydroisojasmone (XXXVII) were treated with N-bromosuccinimide in carbon tetrachloride to obtain the corresponding bromoketones (XXXVIII) and (XXXIX). These bromo compounds were very unstable to heat, hence excessive heating during reaction and subsequent work-up was avoided and the bromo compounds were immediately dissolved in



SCHEME 6

acetone-water (60:40) and solvolyzed by the addition of equivalent amount of aqueous solution of silver perchlorate. It resulted in spontaneous precipitation of silver bromide and the carbonium ion thus formed, underwent solvolysis giving the corresponding hydroxy-enones (V) and (XXXI) respectively, in about 30-35% yields, identical in all respects (TLC, IR, UV, PMR) with V and XXXI obtained above.

The hydroxyenone (V) could be converted into various PGs and PG-analogues by conjugate addition reactions, which have been well established during recent years.

Experimental Procedure

Recorded temperatures are uncorrected. UV spectra (λ_{max} in nm; ε values in parentheses) were recorded on a Perkin-Elmer model 402 UV-visible spectrophotometer, IR Spectra (ν_{max} in cm^{-1}) on a Perkin-Elmer model 237-B infrared spectrophotometer and PMR spectra (chemical shifts in δ-scale) on a Varian T-60 instrument with TMS as an internal standard. Anhydrous Na_2SO_4 was used for drying, unless otherwise stated.

Methyl 10,11-*dihydroxyundecanoate* (*X*)

To a well-stirred mixture of pre-distilled undecylenic acid (VI, 276 g), AcOH (1450 ml) and H_2SO_4 (98%; 20 ml) at 25°, was added H_2O_2 (28% w/v, 240 ml) in portions during 1 hr with external cooling (40°). After the heat of reaction had subsided, the temperature of the mixture was maintained at 40° for 7 hr and then left at room temperature overnight. It was cooled to 20° and $NaHSO_3$ (100 g) added to destroy the excess of peroxide, diluted with cold water (3 litres) and extracted with ether (5 × 500 ml). The combined ether extract was washed with water till neutral, dried and the solvent removed to obatain the mixture of hydroxy-acetoxy compounds (VII + VIII; 315 g); IR(liquid film): 3200 (*b*, COOH), 2900, 2840, 2600, 1735 ($OCOCH_3$) 1700 (COOH), 1450, 1425, 1370, 1225, 1080, 1040 and 950.

This mixture (VII + VIII) was treated with NaOH (120 g) in 80% aq MeOH (2 litres) and refluxed for 5 hr on a steam-bath. MeOH was removed by distillation under reduced pressure and the residue poured into an excess of cold (below 20°) dil. HCl (3*N*) with stirring. The mixture was further cooled to 5° and the precipitated solid filtered off and washed with cold water till neutral. The white solid thus obtained was dried over P_2O_5 *in vacuo* to obtain crude 10,11-dihydroxyundecanoic acid (IX, 220 g). It was dissolved in minimum quantity of ethanol (95%) at 40°, diluted with water to form turbidity, redissolved by warming to 45° (temperature was kept below 45° to avoid polymerization) and kept in the deep freeze overnight.

The crystalline solid obtained was dried over P_2O_5 *in vacuo* (1 mm) to afford pure IX (115 g), m.p. 84-85° (lit.[20] m.p. 85-86°).

The acid (IX, 50 g) was treated with dry methanolic HCl (5%, 400 ml) and kept at room temperature for two days. Excess of MeOH was removed under reduced pressure, the residue treated with excess of saturated aq $NaHCO_3$, extracted with ether, washed with water, dried, ether removed and the residue dried over P_2O_5 *in vacuo* to give the ester (X, 52.5 g) as a semisolid; IR(nujol): 3460 (over tone), 3200 (*b*, OH), 2910, 2850, 1730 ($COOCH_3$), 1450, 1435, 1410, 1370, 1360, 1320, 1265, 1240, 1170, 1170, 1115, 1065, 1045, 1000, 960, 865 and 720 (Found: C, 61.7; H, 10.3. $C_{12}H_{24}O_4$ requires C, 62.0; H, 10.4%).

Methyl 9-formylnonanoate (XI)

The hydroxy ester (X, 50 g) was dissolved in EtOH (500 ml) at 35° and $NaIO_4$ (52 g) in water (450 ml) was added to it during 20 min. It was stirred at 35° for additional 1 hr, the precipitated $NaIO_3$ filtered off and washed with EtOH. The filtrate, alongwith washings, was diluted with equal amount of water, extracted with ether (3 × 250 ml), washed with water (2 × 500 ml), brine (1 × 300 ml) and dried. Ether was evaporated and the residue (40.5 g) distilled at 120-30°/3 mm to yield pure XI (38 g), n_D^{20} 1.4410 (lit.[7] n_D^{20} 1.4410); IR (liquid film): 2920, 2950, 2715 (CHO), 1730 ($-COOCH_3$), 1712 ($-CHO$), 1450, 1430, 1350, 1250 1170, 1090, 1000, and 850) (Found: C, 65.9; H, 9.8. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%); semicarbazone derivative (ethyl acetate) m.p. 98-99° (lit.[7] m.p. 98-100°) (Found: N, 15.9. $C_{12}H_{23}N_3O_3$ requires N, 16.3%); 2,4-DNP derivative, m.p. 86-87° (lit.[21] m.p. 86-87°) (Found: N, 14.9. $C_{17}H_{24}N_4O_6$ requires N, 14.7%).

2-Dodecendioic acid (XIII)

To a cooled solution of malonic acid (110 g) in dry pyridine (100 g), XI (88 g) was added slowly in portions with shaking in about 10 min, and left at room temperature for 24 hr. It was then heated on a steambath for 4 hr, pyridine removed under reduced pressure, the residue diluted with water and extracted with ether (4 × 250 ml). The extract was washed with cold dil. HCl followed by water (2 × 200 ml). It was then extracted with excess of saturated aq Na_2CO_3 and aqueous extract acidified with HCl to yield the half-ester 1-decene-10-carbomethoxy-1-carboxylic acid (XII, 101 g); IR(in Nujol): 3050 (COOH), 2900, 2850, 2600, 1725 ($COOCH_3$), 1680 (Carboxylic CO), 1645 (C=C), 1470, 1435, 1412, 1370, 1330, 1290, 1280, 1240, 1170, 1050, 975, 935, 915, 880, 870, 830 and 720.

The mono ester (XII, 50 g) was treated with aq NaOH (10%, 250 ml), heated on a steam-bath for 4 hr, cooled to room temperature, acidified with conc HCl, the precipitated solid collected and crystallized from acetone to afford the pure, colourless, crystalline XIII (40 g), m.p. 165-66° (lit.[22] m.p. 165-66°); IR (in nujol): 3050 ($-COOH$), 2940, 2845, 2650, 1685 (carboxyl CO), 1640, ($-CH=CH-$), 1460, 1410, 1375, 1300, 1250, 1175, 1070, 980, 940, 865 and 720; UV (MeOH): 213 (12,800) (Found: C, 63.0; H, 8.9. Calc. for $C_{12}H_{20}O_4$: C, 63.1; H, 8.8%).

Lactonization of 2-dodecenoic acid (XIII): Formation of γ-lactone (XIV)

The acid (XIII, 50 g) was heated with 60% H_2SO_4 (1000 ml) at 130° for 2.5 hr in an oil-bath. The reaction mixture was cooled to 15°, diluted with cold water, extracted with ether (3 × 700 ml), washed with water repeatedly till the extract was free from H_2SO_4 and dried. The solvent was removed and the residue distilled at 190-95° (bath)/0.4 mm to furnish the pure XIV (23 g); IR (liquid film): 3100 ($-COOH$), 2920, 2850, 2600, 1765 (γ-lactone), 1695 (carboxyl CO), 1455, 1410, 1350, 1300, 1275, 1235, 1175, 1015, 960, 910, 790 and 720 (Found: C, 62.8; H, 8.6. $C_{12}H_{20}O_4$ requires C, 63.1; H, 8.8%).

Cyclodehydration of XIV: Formation of 2-(ω-carboxyhexyl)cyclopentenone (XV)

Polyphosphoric acid was prepared by gradual addition of P_2O_5 (700 g) with shaking and cooling under tap water to H_3PO_4 (sp. gr. 1.85, 420 ml) under anhydrous conditions. The mixture was heated in an oil-bath at 125-30° for 2 hr with mechanical stirring and then cooled. A mixture containing polyphosphoric acid [270 g; prepared from P_2O_5 (700 g) and H_3PO_4 (420 ml)] and the γ-lactone (XIV, 30 g) was heated in an oil-bath at 100° for 2.5 hr with stirring. The reaction mixture was decomposed by pouring it onto crushed-ice with stirring and extracted with ether (4 × 250 ml). The combined ether extract was washed with water and shaken with 5% aq NaOH. The alkaline extract was acidified with HCl, extracted with ether (2 × 250 ml), washed with water and brine till neutral and dried. Ether was removed on a steam-bath and the residue distilled at 140-45° (bath)/0.4 mm to yield XV (21 g) as a colourless liquid, pure enough for the practical purposes.

For analytical purpose, a portion of it was purified by column chromatography and redistilled at 140-45°/0.4 mm to afford pure sample of XV; IR (liquid film): 3200 (COOH), 2910, 2850, 2600, 1695 (*b*, cyclopentenone and carboxyl CO), 1620 ($-C=CH-$), 1455, 1430, 1400, 1340, 1250, 1170, 1125, 1080, 995, 910, 790 and 720; UV(MeOH): 223 (9,980) (Found: C, 68.4; H, 8.8. $C_{12}H_{18}O_3$ requires C, 68.5; H, 8.6%).

2-(ω-Carbomethoxyhexyl)cyclopentenone (IV)

The acid (XV; 27.5 g) was dissolved in dry

methanolic HCl (15%, 300 ml), left at room temperature for 30 hr, HCl neutralized with solid Na_2CO_3 and MeOH removed on a water bath (60°) under reduced pressure. The residue was diluted with water, extracted with ether (3 × 250 ml), washed with water, brine and dried. Solvent was removed and the residue distilled at 135-40° (bath)/0.4 mm to obtain the pure IV (22.5 g); IR(liquid film): 2915, 2850, 1730 ($COOCH_3$), 1695 and 1630 (cyclopentenone), 1455, 1435, 1405, 1360, 1250, 1170, 1130, 1090, 1050, 1000, 920, 875 and 725; UV(MeOH): 228 (9,100); PMR(CCl_4): 1.38 (*bs*, 8H, $-(CH_2)_4-$), 1.8 to 2.7 (complex, 8H, active $-(CH_2)-$), 3.63 (*s*, 3H, $COOCH_3$) and 7.23 (*m*, 1H, vinyl) (Found: C, 69.3; H, 8.6. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%); semicarbazone (MeOH): m.p. 169-70° (Found: N, 14.9. $C_{14}H_{23}N_3O_3$ requires N, 14.9%).

$NaBH_4$ reduction of IV

To a cooled and stirred solution of IV (10 g) in MeOH (300 ml), $NaBH_4$ (5.8 g) was added at regular intervals during 4 hr. After stirring for additional 2 hr, it was acidified with HCl (10%), diluted with equal amount of water, extracted with ether (3 × 100 ml), washed with 5% aq $NaHCO_3$, water and dried. Solvent was removed and the residue distilled at 140-45° (bath)/0.2 mm to obtain the pure alcohol (XVI, 9.62 g) as a colourless liquid; IR(liquid film): 3450 (*b*, OH), 2920, 2850, 1730 ($COOCH_3$), 1445, 1425, 1350, 1245, 1185, 1160, 1000, 900, 860 and 710 (Found: C, 68.2, H, 10.6. $C_{13}H_{24}O_3$ requires C, 68.4; H, 10.6%); acetate (XVIII) (Ac_2O/Py), b.p. 140-50° (both)/0.4 mm; yield 9.8 g from XVI (9.5 g); IR(liquid film): 2920, 2850, 1725 ($COOCH_3$ and OAc), 1425, 1450, 1360, 1250, 1185, 1160, 1005 and 720; PMR(CCl_4): 1.97 (*s*, 3H, $OCOCH_3$) and 3.6 (*s*, 3H, $-COOCH_3$) (Found: C, 66.2; H, 9.6. $C_{15}H_{26}O_4$ requires C, 66.6; H, 9.7%).

Keto-acetate (XX) from XVII

The acetate (XVII, 9.5 g) was treated with NaOH (4 g), dissolved in 85% aq MeOH (120 ml) and refluxed on a steam-bath for 2.5 hr. Methanol was removed by distillation, residue acidified with dil. HCl, extracted with ether, washed with water and solvent removed to get the hydroxy acid (XVIII, 7.8 g).

To an ice-cooled solution of XVIII (7.8 g) in acetone (125 ml), Jones' reagent, prepared from CrO_3 (4 g), water (11.5 ml) and conc. H_2SO_4 (3.5 ml), was added dropwise during 5 min. It was further stirred for 30 min at 0 to 5°, excess of the reagent destroyed by the addition of *i*-PrOH (15 ml) and worked-up to afford the keto acid (XIX, 7 g). It was distilled at 130-35° (bath)/0.2 mm to obtain the pure keto acid (XIX, 6.2 g) as a colourless liquid; IR (liquid film): 3150, 2930, 2860, 2650, 1735 (cyclopentanone), 1705 (−COOH), 1460, 1435, 1410, 1275, 1250, 1170, 1100, 1030, 925, 820 and 715 (Found: C, 68.0; H, 9.7. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%).

The ethereal solution of the keto acid (XIX, 0.2 g) was esterified with diazomethane to furnish the keto-acetate (XX, 0.18 g), b.p. 135-40° (bath)/0.4 mm; IR(liquid film): 2920, 2850, 1730 (cyclopentanone and $-COOCH_3$), 1450, 1430, 1370, 1245, 1190, 1160, 1090, 1005, 940, 870 and 820 (Found: C, 69.7; H, 10.0. $C_{13}H_{22}O_3$ requires C, 70.0; H, 9.8%).

Regeneration of synthon IV from keto acid (XIX)

To a solution of XIX (6 g) in CCl_4 (50 ml), Br_2 (1.6 ml) in CCl_4 (100 ml) was added during 15 min and stirred at room temperature for 2 hr. Excess of Br_2 was destroyed by shaking the mixture with aq Na_2SO_3, washed with brine, dried and solvent removed to obtain the bromo ketone (XXI, 8.7 g).

A solution of XXI (8.7 g) and NaOH (3.8 g) in water (50 ml) was heated on a steam-bath for 6 hr. It was cooled, diluted with equal quantity of water, acidified with conc. HCl, extracted with ether, washed with brine, dried and solvent removed to yield the keto acid (XXII, 6.1 g). This was then esterified with diazomethane to obtain ester IV (6 g), identical with IV prepared above.

Aluminium isopropoxide reduction of IV

A solution of IV (9.5 g) and freshly distilled aluminium isopropoxide (29 g) in anhydrous *i*-PrOH (250 ml) was refluxed slowly for 20 hr. Solvent was distilled continuously at a very slow rate during the above period, keeping the volume in the reaction flask constant by addition of fresh, dry *i*-PrOH at regular intervals of 30 min. At the end of the reaction, *i*-PrOH was removed by distillation under reduced pressure, the residue taken up in ether and washed with 2*N* HCl and brine till neutral, dried and evaporated to afford a yellowish liquid (11.6 g). It was passed through a neutral silica gel column. After eluting the less polar impurities, the elution with 10% EtOAc-pet. ether gave the pure alcohol (XXIII, 9.2 g), IR(liquid film): 3400 (−OH), 3020, 2970, 2930, 2850, 1740 (ester CO), 1645 (−C=CH−), 1475, 1380, 1250, 1185, 1150, 1120 (−OH), 1050, 960, 920, 825 and 750 (Found: C, 70.7; H, 10.3. $C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3%).

The acetate (XXIV) of XXIII (10 g) was prepared as usual (Ac_2O/Py) and the product distilled at 140-50° (bath)/0.1 mm to yield pure XXIV (10.2 g); IR(liquid film): 3020, 2960, 2920, 2845, 1735 ($-OCOCH_3$ and $-COOCH(CH_3)_2$), 1645 (−C=CH−), 1450, 1430, 1375, 1250, 1175, 1140, 1110, 1025, 950, 910, 880, 820 and 720; PMR(CCl_4): 1.2 [*d*, J=6 Hz, 6H, $-CH(CH_3)_2$], 1.96 (*s*, 3H, $OCOCH_3$), 4.9 (*h*, J=6 Hz, 1H, $-CH(CH_3)_2$), 5.15 (*m*, 1H, −CHOAc) and 5.57

(*m*, 1H, vinyl) (Found: C, 68.7; H, 9.8. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%).

t-Butyl chromate oxidation of the acetate (XXIV)

t-Butyl chromate[14] prepared from CrO_3 (18 g) in CCl_4 was added dropwise during 1 hr to a stirred solution of XXIV (12 g) in CCl_4 (100 ml). The resulting mixture was refluxed at 80±2° with continuous stirring for 24 hr, cooled at 20°, oxalic acid (40 g) in water (100 ml) added cautiously during 1 hr and stirred for 2 hr. The organic layer was separated and the solvent removed on a steam-bath. The aqueous layer was extracted with ether (3 × 100 ml). The residue of the organic layer and the ether extract were mixed, washed with brine, dried and solvent removed to obtain a reddish oily residue (13.7 g).

The major product of the above mixture was isolated first by column chromatography over neutral silica gel (elution with 10% EtOAc-pet. ether) followed by distillation under reduced pressure to obtain the pure keto acetate (XXV, 3.8 g), b.p. 160-70° (bath)/0.2 mm; IR(liquid film): 3020, 2920, 2850, 1730 (OAc, $COOCH(CH_3)_2$), 1685 and 1620 (cyclopentenone), 1460, 1410, 1370, 1230, 1175, 1105, 1030, 950, 880 and 820; UV(MeOH): 24.5 (12,050); PMR(CCl_4): 1.2 [*d*, *J*=6 Hz, 6H, $-OCH(CH_3)_2$], 2.07 (*s*, 3H, $-OCOCH_3$), 4.93 (*h*, *J*=6 Hz, 1H, $-OCH(CH_3)_2$), 5.51 (*m*, 1H, $-CHOAc$) and 5.8 (*m*, 1H, vinyl) (Found: C, 65.5; H, 8.5. $C_{17}H_{26}O_5$ requires C, 65.8; H, 8.4%).

Aluminium isopropoxide reduction of XXVI to isomeric alcohols (XXVII)

A solution of XXVI (5 g) and freshly distilled aluminium isopropoxide (10 g) in anhydrous *i*-PrOH (75 ml) was heated at 80-90°. The *i*-PrOH was distilled slowly during 6 hr, keeping the volume of the reaction mixture constant by addition of fresh, dry *i*-PrOH at regular intervals of 15 min. The reaction mixture was worked-up, following the usual procedure described earlier to afford a yellow oily residue (4.1 g), which was found to a mixture of isomeric alcohols (XXVII, 2.1 g). This was purified by column chromatography; IR(liquid film): 3400 (−OH), 2965, 2920, 2850, 1725 ($OCOCH_3$), 1460, 1450, 1405, 1370, 1250, 1180, 1100 (−OH), 1050, 950, 920 and 810.

Isomeric acetoxytetrahydropyranyloxy compounds (XXVIII)

To a solution of the isomeric alcohols (XXVII, 1.8 g) in dry benzene (50 ml), dihydropyran (1.5 ml) and $POCl_3$ (1 drop) were added and stirred at room temperature for 90 min. The mixture was treated with a few drops of $(Et)_3N$ and the resulting solution washed with brine and dried. Evaporation of the solvent gave a pair of isomeric acetoxytetrahydropyranyloxy compounds (XXVIII, 2.25 g); IR (liquid film): 2960, 2840, 1725 ($OCOCH_3$), 1630, 1460, 1450, 1435, 1375, 1340, 1250, 1190, 1120, 905, 860, 800 and four characteristic bands of tetrahydropyranyloxy group at 1070, 1025, 1010 and 960.

Isomeric mixture of hydroxytetrahydropyranyloxy compounds (XXIX)

NaOH (0.5 g) dissolved in MeOH (20 ml) and water (5 ml) was added to XXVIII (2 g) and the mixture stirred at room temperature for 6 hr. It was diluted with excess of water, extracted with ether (3 × 50 ml), washed with brine, dried and the solvent removed to yield a mixture of isomeric XXIX (1.76 g); IR(liquid film): 3400 (−OH), 3020, 2960, 2840, 1650, 1460, 1450, 1430, 1375, 1340, 1275, 1190, 1150, 1120 (−OH), 1070, 1025, 1010, 960, 900, 860, 800 and 720.

Jones' oxidation of XXIX: Formation of tetrahydropyranyloxyenone (XXX)

A solution of XXIX (1.5 g) in acetone (30 ml) was cooled to −10° and Jones' reagent (0.9 ml) [bulk prepared from CrO_3 (3.5 g), water (10 ml) and conc. H_2SO_4 (3 ml)] was added. It was stirred at −10° for 10 min. The excess of oxidant was destroyed by adding *i*-PrOH (1 ml), diluted with excess of water and extracted with ether (2 × 50 ml). The combined extract was washed with brine, and solvent removed to yield a reddish oily residue (1.3 g). It was purified by column chromatography over neutral alumina to afford pure XXX (0.85 g); IR(liquid film): 2940, 2850, 1700 and 1625 (cyclopentenone), 1465, 1450, 1440, 1375, 1350, 1320, 1260, 1200, 1180, 1160, 1130, 1120, 1070, 1025, 1010, 960, 915, 865 and 810; UV(MeOH): 219 (12,000); PMR(CCl_4): 0.9 (*t*, 3H, $-CH_3$), 4.63 (*bs*, 2H, $-CH_2-O-$), 4.83 (*bs*, 2H, $CH-O-CH-$) and 7.2 (*m*, 1H, vinyl) (Found: C, 72.3; H, 9.9. $C_{16}H_{26}O_3$ requires C, 72.1; H, 9.8%).

Hydroxy-enone (XXXI)

Compound (XXX, 0.7 g) was dissolved in a mixture of AcOH-water-THF (60:25:15, 40 ml) and stirred at room temperature for 8 hr. The reaction mixture was diluted with water (100 ml), extracted with ether (2 × 75 ml), washed with 5% aq $NaHCO_3$, brine, dried and solvent evaporated to give an oily residue (0.45 g). It was passed through a silica gel column and eluted with (20%) EtOAc-pet. ether to obtain pure XXXI (0.3 g); b.p. 150-55° (bath)/0.1 mm; IR(liquid film): 3450 (−OH), 2920, 2850, 1700 and 1625 (cyclopentenone), 1450, 1430, 1350, 1350, 1250, 1190, 1170, 1080 (−OH), 1000, 915 and 720; UV(MeOH): 221 (10,100): PMR(CCl_4): 0.87 (*t*, 3H, CH_3), 1.26 (*bs*, 8H, $-CH_2-$), 4.1 (*bs*, 1H, −CH), 4.8 (*m*, 1H, carbenolic) and 7.13 (*m*,

1H, vinyl) (Found: C, 72.1; H, 10.1. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.9%).

Aluminium isopropoxide reduction of keto acetate (XXV) to alcohol (XXXII)

To a solution of (XXV, 4 g) in dry *i*-PrOH, freshly distilled aluminium isopropoxide (8.4 g) was added and the mixture heated in an oil-bath at 80-90°. The *i*-PrOH was distilled slowly during 6 hr through a short path distillation apparatus keeping the volume of the reaction mixture constant by addition of fresh *i*-PrOH at regular intervals of 15 min. The *i*-PrOH was removed by distillation under reduced pressure and the reaction mixture worked-up as described earlier, to obtain a dark red oil (3.68 g), which was purified by column chromatography over silica gel. Elution with (30%) EtOAc-pet. ether furnished a mixture of two isomeric alcohols (XXXII, 3.25 g) as a pale yellow liquid; IR(liquid film): 3400 (−OH), 2960, 2920, 2850, 1720, (−$OCOCH_3$ and $COOCH(CH_3)_2$), 1610, 1460, 1450, 1410, 1370, 1250, 1180, 1135, 1100 (−OH), 1050, 950, 920, 810 and 715 (Found: C, 65.1; H, 9.2. $C_{17}H_{28}O_5$ requires C, 65.4; H, 9.0%).

Tetrahydropyranyloxy ether (XXXIII) from XXXII

The mixture of alcohols (XXXIII, 3 g) in dry benzene (80 ml) containing dihydropyran (3 ml) and $POCl_3$ (1 drop) was stirred at room temperature for 2.5 hr. It was treated with a few drops of $(Et)_3N$, resulting solution washed with brine and dried. Solvent was removed and the residue (4.8 g) passed through alumina column to obtain pure isomeric tetraanhydropyranyloxy compounds (XXXIII, 3.2 g); IR(liquid film): 2940, 2850, 1725 (ester CO), 1625 (−C=CH), 1460, 1445, 1435, 1370, 1340, 1310, 1250, 1190, 1175, 1120, 1110, 1070, 1025, 1010, 960, 905, 860, 815 and 720.

Tetrahydropyranyloxy-enone (XXXVI) from XXXIII

The above mixture (XXXIII, 3 g) was treated with NaOH (1.2 g) in 10% aq MeOH (30 ml), refluxed for 2 hr, cooled to room temperature, diluted with excess of water and extracted with ether. The aqueous layer was acidified with oxalic acid and extracted with ether (3 × 50 ml), the extract washed with water, brine, dried and solvent removed to give a mixture of two isomeric hydroxytetrahydropyranyloxy acids (XXXIV, 1.86 g).

This mixture (XXXIV, 1.85 g) was dissolved in acetone (80 ml), cooled to −10° and Jones' reagent (2.4 ml) was added dropwise during 5 min. It was further stirred at −10° for 5 min, the excess Jones' reagent destroyed by the addition of *i*-PrOH (5 ml) and the resulting mixture worked-up as usual to yield the keto acid (XXXV, 1.6 g).

The acid (XXXV) was esterified with ethereal solution of diazomethane in the usual manner, the product obtained purified by preparative TLC over silica gel using (25%) EtOAc-benzene as the solvent system to obtain the pure enone (XXXVI, 0.96 g); IR(liquid film): 2940, 2860, 1735, (−$COOCH_3$), 1710 and 1620 (cyclopentenone), 1460, 1450, 1440, 1375, 1355, 1320, 1250, 1250, 1200, 1160, 1125, 1070, 1025, 1010, 960, 870, 810 and 720; UV(MeOH): 223 (10,000); NMR(CCl_4): 3.6 (*s*, 3H, −$COOCH_3$), 4.67 (*m*, 2H, −CH−O−CH−) and 7.16 (*m*, 1H, vinyl) (Found: C, 66.2; H, 8.8. $C_{18}H_{28}O_5$ requires C, 66.6; H, 8.7%).

Hydroxy-enone (V) from XXXVI

The enone (XXXVI, 0.5 g) was dissolved in a mixture of AcOH, water, THF (60:25:15; 30 ml) and stirred at room temperature for 8 hr. The mixture was then diluted with excess of water, extracted with ether (2 × 70 ml), washed with 5% aq $NaHCO_3$ solution, followed by brine and dried. Removal of solvent gave a yellowish oily residue (0.36 g) which was purified by passing through a small silica gel column using (25%) EtOAc-pet. ether as the eluent to obtain the pure V (0.28 g); IR(liquid film): 3410 (−OH), 2910, 2850, 1735 (−$COOCH_3$), 1705 and 1620 (cyclopentenone), 1460, 1440, 1375, 1325, 1250, 1200, 1175, 1040 (−OH), 950, 880, 860 and 720; UV(MeOH): 222 (9,400); PMR(CCl_4): 3.53 (*bs*, 1H, −OH), 3.6 (*s*, 3H, $COOCH_3$), 4.83 (*m*, 1H, −CHOH) and 7.13 (*m*, 1H, vinyl) (Found: C, 64.7; H, 8.4. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%).

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Synthesis of Acridone Alkaloids: Glycocitrine-I, N-Methylatalphylline, Atalphyllidine, 11-Hydroxyacronycine & 11-Hydroxynoracronycine†

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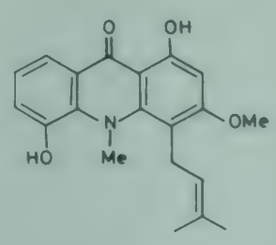
Selective benzylation of 1,3,5-trihydroxyacridone (**3**) results in 5-benzylated acridone (**6**), which on prenylation affords a mixture of monoprenylated acridone (**7**) and diprenylated acridone (**9**). Treatment of **7** with methyl iodide followed by hydrogenolysis furnishes glycocitrine-I (**1**). **9** on benzylation, followed by N-methylation and debenzylation yields N-methylatalphylline (**2**). Condensation of **6** with 3-hydroxyisovaleraldehyde dimethylacetal results in **15**, which on hydrogenolysis furnishes atalphyllidine (**12**). **15** on methylation affords N-methylacridone (**16**) and N,O-dimethylacridone (**17**). Compounds **16** and **17** on hydrogenolysis afford 11-hydroxynoacronycine (**13**) and 11-hydroxyacronycine (**14**), respectively.

After the discovery of broad spectrum antitumor activity of acronycine[1], considerable interest has been shown in the synthesis of acronycine analogs as well as isolation of several new acridones from Rutaceae species. Acridone alkaloids, glycocitrine-I (**1**) was isolated from *Glycosmis citrifolia*[2,3] while N-methylatalphylline (**2**) and atalphyllidine (**12**) were isolated from *Atlantia monophylla*[4,5] and 11-hydroxynoracronycine (**13**) from *A. ceylanica*[6]. The structures assigned to **1**, **2**, **12** and **13** were heavily based on spectral data and chemical transformations. In the present paper we wish to report the synthesis of all these alkaloids along with 11-hydroxyacronycine[7] (**14**) which is a metabolite of acronycine in mammalia.

Acridone alkaloids are weak bases and their N-methylation by heating with HCHO and HCO_2H is not possible. This method of N-methylation is widely used in other alkaloids. It is, therefore, necessary to protect the phenolic hydroxy groups before N-methylation in polyhydroxy acridones by other methods. Methyl, methoxymethyl ether and benzyl groups are most commonly employed for blocking phenolic hydroxy group. Selective alkylation can often be achieved in polyhydric phenols. Whereas in flavones and xanthones alkylation of the hydroxy group *para* to the carbonyl group (most acidic) is very facile, same is not true with the chelated hydroxy group, which undergoes alkylation rather very slowly[8]. Acridones have some structural similarities with flavones and xanthones. With a view to identifying the most easily alkylated hydroxy function in 1,3,5-trihydroxy-acridone (**3**), its selective methylation was carried out using different methylating agents, such as, diazom-



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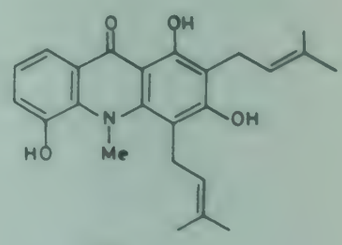

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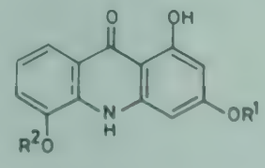
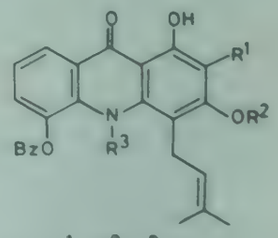
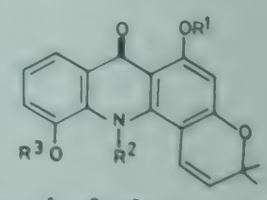


(3) $R^1 = R^2 = H$
(4) $R^1 = H$, $R^2 = Me$
(5) $R^1 = R^2 = Me$
(6) $R^1 = H$, $R^2 = Bzl$



(7) $R^1 = R^2 = R^3 = H$
(8) $R^1 = H$, $R^2 = R^3 = Me$
(9) R^1 = DMA*, $R^2 = R^3 = H$
(10) R^1 = DMA, R^2 = Bzl, $R^3 = H$
(11) R^1 = DMA, R^2 = Bzl, $R^3 = Me$

* DMA = DIMETHYL ALLYL



(12) $R^1 = R^2 = R^3 = H$
(13) $R^1 = R^3 = H$, $R^2 = Me$
(14) $R^1 = R^2 = Me$, $R^3 = H$
(15) $R^1 = R^2 = H$, $R^3 = Bzl$
(16) $R^1 = H$, $R^2 = Me$, $R^3 = Bzl$
(17) $R^1 = R^2 = Me$, $R^3 = Bzl$

† CDRI Communication No. 3784.

ethane, dimethyl sulphate and methyl iodide. With these reagents **3** always gave 1,3-dihydroxy-5-methoxyacridone (**4**) as the major product along with small amount of **5**. On the other hand demethylation of 1-hydroxy-3,5-dimethoxy-acridone (**5**) using basic reagent (piperidine/water) as well as acidic reagent (sulphuric acid) gave **4** as the major compound. Based on the above experience 5-hydroxy function in **3** was selectively protected by benzyl group. The resulting **6** turned out to be the key intermediate for the synthesis of all acridone alkaloids reported in this paper.

1,3,5-Trihydroxyacridone[9] (**3**) was synthesised by the condensation of 3-hydroxyanthranilic acid with phloroglucinol. Selective benzylation of **3** using benzyl chloride, $NaHCO_3$ and NaI in refluxing acetone gave 1,3-dihydroxy-5-benzyloxyacridone (**6**). That the benzyl group in **6** occupied position-5 was supported by the PMR data in which the H-6, H-7 and H-8 signals appeared downfield as compared to those in **3**. Moreover prenylation of **6** using 2-methyl-3-buten-2-ol in the presence of BF_3 etherate resulted in the formation of the C-4 prenylated acridone (**7**) and diprenylated (C-2 and C-4) acridone (**9**) and not the C-6 prenylated derivative. Benzylation at 1-hydroxy group was not expected due to its chelation with the carbonyl function and 3-benzyloxy compound with a free hydroxy group at C-5 would have given rise to C-6 prenylated acridone during prenylation. The position of prenyl group in **7** was confirmed by its PMR spectrum which showed no H-4 signal which usually resonate in the δ 6.4 to 6.8 region[10,11]. In the same manner the position of two prenyl groups in **9** at C-2 and C-4 was evidenced by PMR spectrum which showed the absence of H-2 and H-4 protons signals generally appearing between δ 6.0 and 6.8 (ref. 10,11).

Methylation of **7** using methyl iodide and K_2CO_3 in acetone under reflux gave the N,O-dimethylated acridone (**8**). Various attempts for the debenzylation of **8** to **1** with several reagents such as, (i) 10% aq HCl, (ii) HCl in $AcOH$, (iii) TFA, (iv) catalytic hydrogenation (10% Pd-C) at room temperature, (v) transfer hydrogenation using (a) 10% Pd–C and HCO_2H in MeOH and (b) 10% Pd–C and cyclohexene in methanol proved abortive. However, hydrogenolysis[12] of **8** using 10% Pd–C containing NaOEt in abs EtOH under reflux afforded glycocitrine-I (**1**). The spectral data of synthetic glycocitrine-I were in complete agreement with those reported for the natural material[2,3].

Benzylation of the acridone (**9**) using benzyl chloride, K_2CO_3 and NaI in EtOH under reflux afforded 1-hydroxy-3,5-dibenzyloxy-2,4-diprenyl-acridone (**10**) as an oil. Methylation of **10** with methyl iodide gave the N-methylated acridone (**11**). Debenzylation of **11** using NaOEt and 10% Pd–C in abs ethanol under reflux furnished N-methylatalphylline (**2**), the spectral data of which were found identical (UV, IR, PMR and MS) with those of the natural sample[4].

The synthesis of atalphyllidine (**12**), 11-hydroxynoracronycine (**13**) and 11-hydroxyacronycine (**14**) were carried out in good yields. Condensation of **6** with 3-hydroxyisovaleraldehyde dimethylacetal in pyridine gave **15**. The appearance of two doublets ($J = 10.0$ Hz) at δ 5.45 and 6.25 in the PMR spectrum of **15** and also intense peak at m/z 384 (M^+-15, 100%) in its mass spectrum, characteristic of 2,2-dimethylchromene[13,14] function confirmed the presence of this system in **15**. That the chromene ring was angularly fused was evidenced by its PMR spectrum, which showed H-2 signal at δ 6.24 and the absence of H-4 signal. Hydrogenolysis of **15** with 10% Pd–C and NaOEt in EtOH furnished atalphyllidine[5] (**12**). Methylation of **15** by methyl iodide under reflux for 12 hr afforded a mixture of N-methylacridone (**16**) and N,O-dimethylacridone (**17**). Hydrogenolysis of **16** and **17** gave 11-hydroxynoracronycine[6] (**13**) and 11-hydroxy-acronycine[7] (**14**) respectively.

Experimental Procedure

All m.ps are uncorrected. The IR spectra were recorded in KBr or neat on Perkin-Elmer 557 or Beckmann Acculab-I instrument and UV spectra in methanol on Hitachi model 320 instrument. The PMR spectra were taken either at 90 MHz on a Perkin-Elmer R-32 or at 80 MHz on CFT-20 or at 400 MHz on Brucker WM 400 instrument using TMS as an internal reference; chemical shifts are expressed in δ units. Mass spectra were taken on a Jeol D-300 spectrometer fitted with a direct inlet system. Silica gel was used as an adsorbent for PLC purification. All new compounds were analysed for C, H and N. The results were in agreement within the accepted values (± 0.3%).

1,3-*Dihydroxy*-5-*methoxyacridone*[10] (4)

Method A

A mixture of **5** (40 mg), piperidine (8 ml) and H_2O (2 ml) was stirred under refluxing for 96 hr. It was cooled, acidified with 2*N* HCl and extracted with EtOAc, washed with H_2O, dried (Na_2SO_4) and solvent removed to give a residue, which on PLC purification afforded **4** (12 mg) and **5** (15 mg).

Method B

A solution of acridone **5** (50 mg) in conc. H_2SO_4 (1 ml) was stirred for 12 hr. It was poured on ice (50 g) and extracted with EtOAc, washed with H_2O, dried (Na_2SO_4) and solvent removed. The residue on PLC purification gave acridones **4** (15 mg) and **3** (10 mg).

1-Hydroxy-3,5-dimethoxyacridone (**5**)

A methanolic solution of **4** (1 g) was treated with a ethereal solution of diazomethane (50 ml) (prepared from 1.5 g of nitrosomethyl urea) at 0°. After 12 hr usual work-up afforded **5** (900 mg), m.p. 208-10° ($CHCl_3$ – MeOH); IR:3375, 1650, 1625 and 1585 cm^{-1}; PMR (acetone-d_6): 3.82 and 4.02 (each *s*, 6H, 2 × $-OCH_3$), 6.12 (*d*, 1H, H-2, J = 2.0 Hz), 6.86 (*d*, 1H, H-4, J = 2.0 Hz), 7.14-7.34 (*m*, 2H, H-6 and H-7) and 7.73 (*dd*, 1H, H-8, J = 8.0 and 2.0 Hz); MS: *m/z* 271 (M^+) and 256 (M^+-15).

1,3-Dihydroxy-5-benzyloxyacridone (**6**)

A mixture of **3**[9] (6 g), benzyl chloride (2.3 ml), acetone (600 ml), $NaHCO_3$ (30 g) and NaI (1 g) was refluxed for 18 hr. The solution was filtered and solvent removed *in vacuo* to give a crude product (6 g), which was chromatographed over a column of silica gel using $CHCl_3$ – MeOH (98:2) as eluant to afford **6** (4g), m.p. 237-38° ($CHCl_3$); UV: 255, 268 (sh), 286, 296 (sh), 328 (sh) and 390 (br) nm; IR: 3560, 3300, 3200, 1645 and 1600 cm^{-1}; PMR (acetone-d_6): 5.20 (*s*, 2H, $PhCH_2O-$), 6.05 (*d*, 1H, H-2, J = 2.0 Hz), 6.45 (*d*, 1H, H-4, J = 2.0 Hz), 7.05-7.50 (*m*, 7H, H-6, H-7 and C_6H_5-) and 7.75 (*dd*, 1H, H-8, J = 8.0 and 2.0 Hz); MS: *m/z* 333 (M^+) and 242 (M^+-91).

1,3-Dihydroxy-4-(3,3-dimethylallyl)-5-benzyloxyacridone (**7**) *and* *1,3-dihydroxy-2,4-bis(3,3-dimethylallyl)-5-benzyloxyacridone* (**9**)

To a stirred solution of **6** (1 g) and 2-methyl-3-buten-2-ol (1 ml) in dioxane (100 ml) was added gradually BF_3 etherate (1 ml). After 2 hr the reaction mixture was diluted with water (200 ml), extracted with ethyl acetate (4 × 50 ml), dried (Na_2SO_4) and solvent removed to give a residue which was chromatographed over a column of silica gel. Elution with $CHCl_3$ gave **9** (200 mg), m.p. 155-56° (CH_2Cl_2-hexane); UV: 240, 250, 292, 304, 372 and 390 (br) nm; IR: 3420, 3285, 1630 and 1595 cm^{-1}; PMR (acetone-d_6): 1.60 and 1.80 [each *s*, 12H, 2 × $=C(CH_3)_2$], 3.50 (*m*, 4H, 2 × $-CH_2-CH=$), 5.00 (*m*, 2H, 2 × $-CH=$), 5.32 (*s*, 2H, $PhCH_2O-$), 7.00-7.50 (*m*, 7H, H-6, H-7 and C_6H_5-) and 7.65 (*dd*, 1H, H-8, J = 8.0 and 2.0 Hz); MS: *m/z* 469 (M^+), 468, 467 and 321.

Further elution with $CHCl_3$ – MeOH (98:2) furnished **7** (300 mg), m.p. 247-48° (acetone); UV: 235 (sh), 248, 298 (br) and 372 (br) nm; IR: 3330, 1635, 1600 and 1560 cm^{-1}; PMR (acetone-d_6): 1.60 [*s*, 6H, $=C(CH_3)_2$], 3.52 (*d*, 2H, $-CH_2-HC=$, J = 7.0 Hz), 5.05 (*m*, 1H, $-CH=$), 5.35 (*s*, 2H, $PhCH_2O-$), 6.30 (*s*, 1H, H-2), 7.00-7.50 (*m*, 7H, H-6, H-7 and C_6H_5-) and 7.70 (*dd*, 1H, H-8, J = 8.0 and 2.0 Hz); MS: *m/z* 401 (M^+), 333 and 310.

5-Benzyloxy-1-hydroxy-3-methoxy-4-(3,3-dimethylallyl)-N-methylacridone (**8**)

A mixture of **7** (100 mg), acetone (25 ml), methyl iodide (2 ml) and K_2CO_3 (1 g) was stirred and refluxed for 12 hr. The reaction mixture was filtered and solvent removed. The residue on PLC afforded **8** (40 mg), m.p. 115-16° ($CHCl_3$); UV: 225, 265, 335 and 405 (br) nm; IR: 3420, 1615 and 1585 cm^{-1}; PMR ($CDCl_3$): 1.55 [*s*, 6H, $=C(CH_3)_2$], 3.30 (*d*, 2H, $-CH_2-CH=$, J = 7.0 Hz), 3.44 (*s*, 3H, $N-CH_3$), 3.80 (*s*, 3H, $-OCH_3$), 5.05 (*s*, 2H, $PhCH_2O-$), 5.15 (*m*, 1H, $-CH=$), 6.24 (*s*, 1H, H-2), 7.00-7.17 (*m*, 2H, H-6 and H-7), 7.20-7.40 (*m*, 5H, C_6H_5-) and 7.78 (*q*, 1H, H-8, J = 6.0 and 3.0 Hz); MS: *m/z* 429 (M^+), 428, 414 and 413.

Glycocitrine-I (**1**)

A solution of **8** (30 mg), NaOEt (60 mg) in abs ethanol (15 ml) and 10% Pd – C (30 mg) was refluxed for 30 min. The reaction mixture was filtered and solvent removed to give a residue, which was diluted with water (50 ml), acidified (1*N* HCl) and resultant precipitate filtered off. The residue (precipitate) was purified through PLC to furnish **1** (12 mg), m.p. 209-10° ($CHCl_3$) (lit.[2] 210-12°); UV: 228, 268 (sh), 332 (sh), 336 and 415 (br) nm; IR: 3240, 1630, 1590, and 1565 cm^{-1}; PMR (acetone-d_6): 1.62 and 1.71 [each *s*, 6H, $=C(CH_3)_2$], 3.40 (*d*, 2H, $-CH_2-CH=$, J = 7.0 Hz), 3.58 (*s*, 3H, $N-CH_3$), 3.85 (*s*, 3H, $-OCH_3$), 5.24 (*m*, 1H, $-CH=$), 6.27 (*s*, 1H, H-2), 7.00-7.20 (*m*, 2H, H-6 and H-7) and 7.64 (*dd*, 1H, H-8, J = 8.00 and 2.00 Hz); MS: *m/z* 339 (M^+), 324 (M^+-15), 284, 282 and 271.

3,5-Dibenzyloxy-1-hydroxy-2,4-bis(3,3-dimethylallyl) acridone (**10**)

A mixture of **9** (200 mg), benzyl chloride (100 mg), NaI (25 mg), and K_2CO_3 (200 mg) in acetone (25 ml) was refluxed for 6 hr. The reaction mixture was cooled, filtered and solvent removed. The residue on PLC purification afforded **10** as an oil (50 mg); UV: 262, 306, 320 and 400 (br) nm; IR: 3400, 1630 and 1600 cm^{-1}; PMR ($CDCl_3$): 1.50, 1.55 and 1.65 [each *s*, 12H, 2 × $=C(CH_3)_2$], 3.40 (*br*, 4H, 2 × $-CH_2-CH=$), 4.80-5.30 (*m*, 6H, 2 × $-CH=$ and 2 × $PhCH_2O-$), 6.90-7.05 (*m*, 2H, H-6 and H-7), 7.30 (*s*, 5H, C_6H_5-) and 7.85 (*m*, 1H, H-8); MS: *m/z* 559 (M^+), 556 (M^+-1), 490, 411, 399 and 343.

3,5-Dibenzyloxy-1-hydroxy-2,4-bis(3,3-dimethylallyl)-N-methylacridone (**11**)

A solution of **10** (40 mg), methyl iodide (2 ml) and K_2CO_3 (50 mg) in acetone was refluxed for 12 hr. Usual work-up afforded **11** (25 mg), m.p. 115-17° (CH_2Cl_2-hexane); UV: 265, 322 and 410 (br) nm; IR: 3440, 1620 and 1590 cm^{-1}; PMR ($CDCl_3$): 1.50 and 1.60 [each *s*, 12H, 2 × $=C(CH_3)_2$], 3.40 (*br*, 4H, 2 × $-CH_2-CH$

=), 3.50 (*s*, 3H, N $-CH_3$), 4.80 and 5.07 (each *s*, 4-H, 2 × $PhCH_2O-$), 5.20 (*br*, 2H, 2 × $-CH=$), 7.00-7.40 (*m*, 7H, H-6, H-7 and C_6H_5-) and 7.80 (*m*, 1H, H-8); MS: *m/z* 573 (M^+), 572 (M^+-1), 481, 425 and 411.

N-Methylatalphylline (**2**)

A solution of **11** (25 mg), abs ethanol (25 ml) and NaOEt (50 mg) was refluxed in the presence of 10% Pd −C (25 mg) for 40 min. Usual work-up gave a residue, which on PLC purification furnished **2** (6 mg), m.p. 190-92° ($CHCl_3$) (lit.[4] 192-93°); UV: 228, 260 (sh), 273, 336 and 415 (br) nm; IR: 3500 (br) and 1620 cm^{-1}; PMR ($CDCl_3$): 1.76, 1.82, 1.85 and 1.87 [each *s*, 12H, 2 × $=C(CH_3)_2$], 3.50 (*br*, 4H, 2 × $-CH_2-CH=$), 5.32-5.40 (*m*, 2H, 2 × $-CH=$), 7.10-7.30 (*m*, 2H, H-6 and H-7) and 7.95 (*d*, 1H, H-8, $J=8.0$ Hz); MS: *m/z* 393 (M^+), 378, 350, 338 and 322.

11-*Benzyloxy*-1-*hydroxy*-3,12-*dihydro*-3,3-*dimethylpyrano*[2,3-*c*]*acridin*-7-*one* (**15**)

A mixture of **6** (500 mg) and 3-hydroxyisovaleraldehyde dimethylacetal (0.5 ml) in pyridine (2 ml) was refluxed at 150-60°. Two more portions of the acetal (0.25 ml each) were added after 12 hr, 24 hr and the refluxing continued for another 24 hr (total reflux 48 hr). The reaction mixture was concentrated and the residue chromatographed over a column of silica gel using chloroform as eluant to give **15** (200 mg), m.p. 180-85° (CH_2Cl_2); UV: 210, 259 (sh), 273, 284, 298 and 408 (br) nm; IR: 3420 and 1640 cm^{-1}; PMR ($CDCl_3$): 1.40 [*s*, 6H, $C(CH_3)_2$], 5.18 (*s*, 2H, $PhCH_2O-$), 5.45 (*d*, 1H, H-2', $J=10.0$ Hz), 6.05 (*s*, 1H, H-2), 6.25 (*d*, 1H, H-1', $J=10.0$ Hz), 6.95-7.15 (*m*, 2H, H-6 and H-7), 7.35 (*s*, 5H, C_6H_5-) and 7.75 (*q*, 1H, H-8, $J=6.0$ and 3.0 Hz); MS: *m/z* 399 (M^+), 384 (M^+-15) and 307. Further elution with $CHCl_3$ – MeOH (98:2) gave acridone **6** (200 mg).

Atalphyllidine (**12**)

The acridone (**15**, 50 mg) was debenzylated by the procedure described for **8** to afford **12** (22 mg), m.p. 270-72° (lit.[6] 275°); UV: 258, 270, 295 (sh), 324 (sh) and 400 (br) nm; IR: 3380 and 1640 cm^{-1}; PMR (DMSO-d_6): 1.32 [*s*, 6H, $C(CH_3)_2$], 5.45 (*d*, 1H, H-2', $J=10.0$ Hz), 5.81 (*s*, 1H, H-2), 6.85-7.00 (*m*, 2H, H-6 and H-7), 7.07 (*d*, 1H, H-1', $J=10.0$ Hz) and 7.4 (*m*, 1H, H-8); MS: *m/z* 309 (M^+) and 294 (M^+-15).

11-*Benzyloxynoracronycine* (**16**)

A mixture of **15** (100 mg), methyl iodide (0.5 ml) and K_2CO_3 (100 mg) in acetone (20 ml) was refluxed for 12 hr. Usual work-up followed by purification through PLC afforded **16** (70 mg), m.p. 155° ($CHCl_3$ + hexane); UV: 265, 280, 294, 320 (sh), 342 (sh) and 416 (br) nm; IR: 1625 and 1585 cm^{-1}; PMR ($CDCl_3$): 1.50 [*s*, 6H, $C(CH_3)_2$], 3.70 (*s*, 3H, N $-CH_3$), 5.20 (*s*, 2H, $PhCH_2O-$), 5.45 (*d*, H-2', $J=10.0$ Hz), 6.20 (*s*, 1H, H-2), 6.52 (*d*, 1H, H-1', $J=10.0$ Hz), 7.15-7.30 (*m*, 2H, H-6 and H-7), 7.40 (*s*, 5H, C_6H_5-), and 7.95 (*q*, 1H, H-8, $J=6.0$ and 3.0 Hz); MS: *m/z* 413 (M^+), 398 (M^+-15) and 322; along with 11-benzyloxyacronycine (**17**, 15 mg), m.p. 184-86°, UV: 262, 280, 304 (sh), 330 (sh) and 390 (br) nm; IR: 1630, 1600 and 1560 cm^{-1}; PMR ($CDCl_3$): 1.48 [*s*, 6H, $C(CH_3)_2$], 3.55 (*s*, 1H, N $-CH_3$), 3.90 (*s*, 3H, $-OCH_3$), 5.17 (*s*, 2H, $PhCH_2O-$), 5.48 (*d*, 1H, H-2', $J=10.0$ Hz), 6.25 (*s*, 1H, H-2), 6.55 (*d*, 1H, H-1', $J=10.0$ Hz), 7.10-7.25 (*m*, 2H, H-6 and H-7), 7.40 (*s*, 5H, C_6H_5-) and 7.90 (*q*, 1H, H-8, $J=6.0$ and 3.0 Hz); MS: *m/z* 427 (M^+) and 412 (M^+-15).

11-*Hydroxynoracronycine* (**13**)

By adopting a similar procedure as described for **8** the acridone (**16**, 50 mg) on hydrogenolysis afforded **13** (25 mg), m.p. 250-52° ($CHCl_3$) (lit.[10] 247-54°); UV: 238, 267, 284, 293 (sh), 325, 341 (sh) and 424 (br) nm; IR: 3250 and 1630 cm^{-1}; PMR ($CDCl_3$): 1.51 [*s*, 6H, $C(CH_3)_2$], 3.76 (*s*, 3H, N $-CH_3$), 5.54 (*d*, 1H, H-2', $J=10.0$ Hz), 6.25 (*s*, 1H, H-2), 6.54 (*d*, 1H, H-1', $J=10.0$ Hz), 7.10-7.25 (*m*, 2H, H-6 and H-7) and 7.95 (*q*, 1H, H-8, $J=6.0$ and 3.0 Hz); MS: *m/z* 323 (M^+), 308 (M^+-15) and 293.

11-*Hydroxyacronycine* (**14**)

Hydrogenolysis of **17** (20 mg) gave **14** (10 mg), m.p. 205-7°; UV: 230, 266, 278, 315, 332 (sh) and 390 (br) nm; IR: 3220, 1620, 1605 and 1590 cm^{-1}; PMR ($CDCl_3$): 1.51 [*s*, 6H, $C(CH_3)_2$], 3.67 (*s*, 3H, N $-CH_3$), 3.91 (*s*, 3H, $-OCH_3$), 5.53 (*d*, 1H, H-2', $J=10.0$ Hz), 6.27 (*s*, 1H, H-2), 6.70 (*d*, 1H, H-1', $J=10.0$ Hz), 6.90-7.18 (*m*, 2H, H-6 and H-7) and 7.85 (*m*, 1H, H-8); MS: *m/z* 337 (M^+), 322 (M^+-15) and 307.

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Synthesis of Heterocycles via Enamines: Part XI† – Reactions of 1,4-Dihydropyrimidine-2(3*H*)-thiones/-ones with 1,2- & 1,3-Binucleophiles

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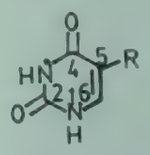
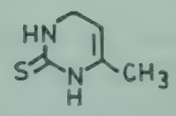
The addition, cleavage and ring transformation reactions of derivatives of 4,4,6-trimethyl-1,4-dihydro-pyrimidine-2(3*H*)-thione/one with hydroxylamine, hydrazine and thiourea are reported.

Pyrimidines, uracil (**1a**) and thymine (**1b**) possess an enaminone chromophore and undergo a variety of ring transformations[1] with nucleophiles which initially react at enaminone α-carbon (C-6). Enamines undergo similar reactions at α-carbon with difficulty and with only strong nucleophiles[2]. We have recently found[3] that 6-methyl-1,4-dihydropyrimidine-2(3*H*)-thione (**2**) undergoes a facile base-catalysed addition of methanol at 5,6-double bond to provide 6-methoxy-6-methyl-1,4,5,6-tetrahydropyrimidine-2(3*H*)-thione (**3**). Compound **2** differs from **1** in being devoid of carbonyl at C-4 and has a thione moiety at C-2 instead of a carbonyl group. It has been reported[4] that derivatives of analogous system **4** react with hydroxylamine hydrochloride in the presence of a base to form oximes[4] (**5**), but **6** and **7** (R = Ph) fail to react. This fact and our observation on the addition of methanol to **2**[3], prompted us to investigate the title reactions using hydroxylamine, hydrazine and thiourea as nucleophiles.



(1a) R=H
(1 b) R=CH_3



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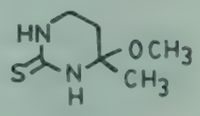

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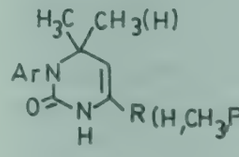

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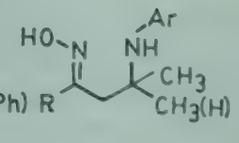

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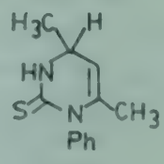

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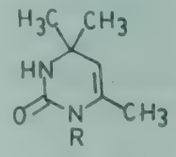
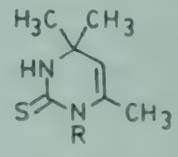


(7)



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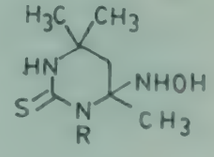


(9)

4,4,6-Trimethyl-1,4-dihydropyrimidine-2(3*H*)-thione (**8**, R = H) (R_f 0.7; $CHCl_3$ – MeOH, 95 : 5) reacted with hydroxylamine hydrochloride in the presence of sodium hydroxide to give a product (R_f 0.3; same solvent), which showed in its mass spectrum the molecular ion peak at *m/z* 189, indicating that it was an adduct of **8** and hydroxylamine. On melting point determination in a capillary tube, the adduct was found to undergo some change around 150°C, before finally melting at the melting point (254-55°) of **8** (R = H). We argued that during this process the adduct decomposed to give the precursor. This was actually found to be so since heating the adduct alone in an oil-bath at 140-50° for 15-20 min gave **8** (R = H) in quantitative yield. Anomalous analytical results, viz. higher % of carbon and lower % of nitrogen may be due to partial decomposition of adduct before combustion. PMR spectrum of the adduct revealed the absence of anamine C_5 – H signal (δ 4.7) of the precursor, presence of a multiplet (δ 1.35-1.65) at an upfield position due to CH_2(C – 5) and the upfield shift of $C_6 - CH_3$ (δ 1.20) compared to that of $C_6 - CH_3$ (δ 1.75) of **8** (R = H). These data indicated that addition had occurred at 5,6-double bond of **8** (R = H). From these data and a hypsochromic shift in UV spectrum of the adduct, as compared to that of **8** (R = H), the adduct has been assigned the structure as 6-hydroxyamino-4,4,6-trimethyl-1,4,5,6-tetrahydropyrimidine-2(3*H*)-thione (**9**, R = H). The adduct is stable towards bases but on stirring its solution in glacial or dilute acetic acid or aq. HCl as well as on heating as

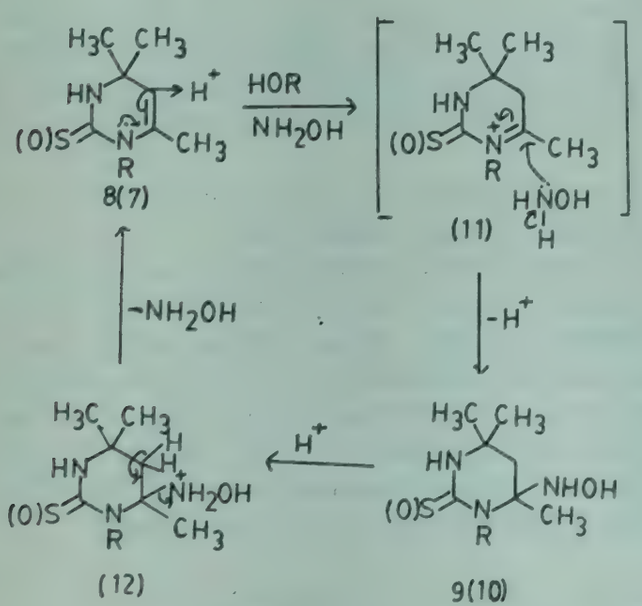
† Part X: Singh H, Singh P & Deep K, *Tetrahedron*, 39 (1983) 1655.

such at 120°C, it gives **8** (R = H). 1-Methyl/phenyl-4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thiones (**8**, R = CH_3/Ph) did not react with hydroxylamine under the above reaction conditions. However, **8** (R = CH_3) reacted with hydroxylamine in ethanol containing sodium ethoxide (2 equiv) to give a white semi-solid product, which from its spectral data could be assigned the structure as 6-hydroxyamino-1,4,4,6-tetramethyl-1,4,5,6-tetrahydropyrimidine-2(3*H*)-thione (**9**, R = CH_3). This compound again decomposed when treated with acid or on heating. Compound (**8**, R = Ph) failed to react with hydroxylamine while **2** furnished a large number of products.

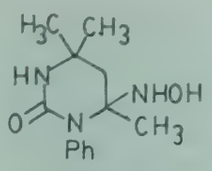
4,4,6-Trimethyl-1,4-dihydropyrimidine-2(3*H*)-one (**7**, R = H) (R_f 0.7; EtOAc) reacted with hydroxylamine hydrochloride to give a product (R_f 0.4; EtOAc) which during work-up got transformed to **7** (R = H). However, the adduct (**10**) of **7** (R = Ph) and hydroxylamine, could be isolated in low yield. On stirring a solution of **10** in acetic acid, **7** (R = Ph) was obtained.

The formation of these adducts, being very slow in aprotic solvents (dioxane and acetonitrile), may be visualised to proceed by protonation at C-5 and attack of the nucleophile at C-6 of intermediary imminium cation (**11**).

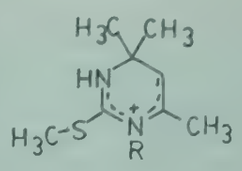
Uracil and its derivatives reacted with hydroxylamine to provide corresponding isoxazolone derivatives[5] but 6-methyl-1,4-dihydropyrimidine-2(3*H*)-thiones (**8**, R = H/CH_3)/ ones (**9**, R = Ph) formed only the addition products which did not undergo any ring transformation. The adducts **9** (R = H) and **10** remained unchanged in bases but in the presence of acids elimination of hydroxylamine occurred to give back the corresponding precursors (Scheme 1).



Scheme 1



(10)



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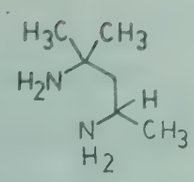

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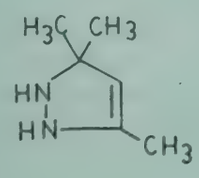

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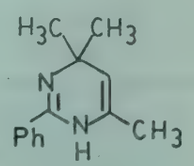

(16)

Derivatives of **7** and **8** with hydrazine decomposed to give mostly volatile products. However, **13** (R = CH_3)[6] with hydrazine in boiling *n*-propanol afforded triaminoguanidine hydroiodide[7] and a liquid product (M^+ 116). The PMR spectrum of the liquid product in $CDCl_3$ exhibited signals at δ 1.20 (*s*, 3H, CH_3), 1.30 (*s*, 3H, CH_3), 1.87 (*d*, 2H, CH_3), 2.35 (*d*, 2H, CH_2), 3.32-4.07 (*b*, 4H, $2NH_2$, exchangeable with D_2O), 4.87 (*b*, 1H, CH). Carbon-13 NMR‡ in $CDCl_3$ exhibited signals at δ 17.1 (*q*, CH_3), 30.1 (*q*, CH_3), 30.3 (*q*, CH_3), 51.1 (*t*, CH_2), 148.6 (*s*, tertiary carbon bearing NH_2). On the basis of these spectral data, the liquid product has been assigned the structure as 2,4-diamino-2-methylpentane (**14**). It gave a diacetyl derivative, m.p. 148° (lit[8] m.p. 162°). Similarly, **13** (R = Ph) reacted with hydrazine to give triaminoguanidine hydroiodide and 2,4-diamino-2-methylpentane (**14**).

These reactions of **13** (R = CH_3/Ph) may be visualised to proceed by a mechanism suggested earlier for a similar reaction[7] of 1,4,6-trimethylpyrimidine-2(1*H*)-thione. The mechanism involves initial formation of triaminoguanidine hydroiodide and 3,5,5-trimethyl-2,5-dihydropyrazole (**15**). Compound (**15**) undergoes reductive cleavage with hydrazine to give **14**.

Thus, in the case of binucleophile such as hydrazine, 1,4-dihydropyrimidinium cations, like uracil derivatives[9], might be undergoing ring transformations to pyrazole derivatives which on further reductive cleavage provide 2,4-diamino-2-methylpentane (**14**). However, 2-phenyl-4,4,6-trimethyl-1,4-dihydropyrimidine (**16**) has been found to react with hydrazine in boiling *n*-propanol solution to give benzoyl-

‡ The signal for CH could not be detected and might be hidden under any other signal.

hydrazine, m.p. 114-17° (lit.[10], 112-16°). It is proposed that hydrazine attacks C-2 of **16** to form tetrahedral intermediate which undergoes hydrolytic cleavage to benzoylhydrazine.

It is reported[11] that 1,3-dimethyluracil undergoes a facile reaction with thiourea to give 2-thiouracil but monomethyluracil fails to react and the reactions of substituted thioureas and 1,3-dimethyluracil take place under drastic conditions. In our hands **8** (R $=CH_3$), a monosubstituted dihydropyrimidine derivative, reacted with thiourea and sodium ethoxide in refluxing dimethylformamide solution to provide 4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thione (**8**, R = H). This reaction was quite slow in ethanol as compared to that in DMF. The reaction could also be performed in the presence of a trace of HCl, but yield of the product was low. Similarly **8** (R = Ph) and **7** (R = H/Ph) also reacted with thiourea to give **8** (R = H) but the rate of reaction decreased when a bulkier group was present at N_1 (Table 1). Arguing that cations should be more reactive toward nucleophiles, **13** (R $=CH_3$/Ph)[7] reacted with thiourea and sodium ethoxide in ethanol solution to provide **8** (R = H) in 90% yield and as expected the reaction was completed in shorter time. But N-substituted thioureas failed to react with **7** (R = H/Ph), **8** (R = H/Ph) and **13** (R $=CH_3$/Ph). These reactions of **7**, **8** as well as **13** with thiourea might proceed by a mechanism proposed for similar reactions of 1,3-dimethyluracil[11].

It may be concluded that 6-methyl-1,4-dihydropyrimidine-2(3*H*)-thione/one derivatives which are devoid of C-4 carbonyl group of uracil derivatives also show reactivity toward nucleophiles. These results point to the probability that such dihydropyrimidine derivatives like biological pyrimidine bases have the potential of being used in ring transformation reactions.

Experimental Procedure

Melting points were determined in capillaries and are uncorrected. PMR spectra were recorded on a Tesla BS 487C 80 MHz instrument using TMS an internal standard, IR spectra on a Hungarian Spectromon 2000 spectrophotometer and mass spectra on a Hitachi-Perkin-Elmer RMU-60D instrument.

Table 1 – Formation of 4,4,6-Trimethyl-1,4-dihydropyrimidine-2(3*H*)-thione (**8**, R = H) from **7**, **8**, **13** and Thiourea

Reactant	DMF/NaOEt		EtOH/NaOEt		EtOH/HCl	
	Time (hr)	Yield (%)	Time (hr)	Yield (%)	Time (hr)	Yield (%)
8(R $=CH_3$)	8	90	50	80	40	65
8(R = Ph)	12	80	70	70	70	60
7(R = H)	5	70	30	60	30	60
7(R = Ph)	8	80	50	70	50	70
13(R $=CH_3$)	—	—	4-5	90	—	—
13(R = Ph)	—	—	4-5	90	—	—

6-Hydroxyamino-4,4,6-trimethyl-1,4,5,6-tetrahydropyrimidine-2(3H)-thione (**9**, *R = H*)

A solution of **8** (R = H) (1.6 g, 0.01 mol), hydroxylamine hydrochloride (2.1 g, 0.03 mol) and sodium hydroxide (1.2 g, 0.03 mol) in *n*-propanol was refluxed for 2 hr, filtered while hot, the filtrate concentrated and cooled to give **9** (R = H) (1.8 g, 95%); m/z 189 (M^+), 156 (189-NH_2OH) (Found C, 48.8; H, 8.0; N, 19.4, $C_7H_{15}N_3OS$ requires C, 44.4; H, 7.9; N, 22.2%); PMR (DMSO-d_6): δ 1.20 (*m*, 9H, $3CH_3$), 1.35-1.65 (*m*, 2H, CH_2), 6.59-6.90 (*b*, 2H, NH_2) and 7.30 (*s*, 1H, CH); IR: 2750 (OH) cm^{-1}; UV (EtOH): 255 nm.

6-Hydroxyamino-1,4,4,6-tetramethyl-1,4,5,6-tetrahydropyrimidine 2(3H)-thione (**9**, *R = CH_3*

A solution of **8** (R = CH_3) (1.7 g, 0.01 mol), hydroxylamine hydrochloride (2.1 g, 0.03 mol) and sodium ethoxide (4.1 g, 0.06 mol) in ethanol was refluxed for 5 hr, filtered while hot and the filtrate concentrated. The residue was chromatographed over silica gel using benzene – ethyl acetate (2:1) as eluant to give **9** (R = CH_3) (50%), semi-solid; *m/z* 203 (M^+), 170 (203 – NHOH), 155 (170 – CH_3); PMR (DMSO-d_6): δ 1.30 (*s*, 6H, $2CH_3$), 1.36 (*s*, 3H, CH_3), 1.50-2.00 (*m*, 2H, CH_2), 3.03 (*s*, 3H, CH_3), 7.43 (*b*, 1H, NH or OH), 7.90 (*b*, 1H, NH, OH); IR: 2800 (OH) cm^{-1}; UV (EtOH): 245 nm [**8** (R = CH_3), UV (EtOH) 255 nm].

6-Hydroxyamino-4,4,6-trimethyl-1-phenyl-1,4,5,6-tetrahydropyrimidin-2(3H)-one (**10**)

Similar reaction with **7** (R = Ph) afforded **10** in 25% yield, m.p. 116-17°; *m/z* 249 (M^+), 216 (249 – NH_2OH); (Found C, 62.8; H, 7.5; N, 17.3; $C_{13}H_{19}N_3O_2$ requires C, 62.7; H, 7.6; N, 16.9%); PMR (TFA): δ 1.6 (*s*, 9H, $3CH_3$), 2.57 (*s*, 2H, CH_2), 3.25 (*b*, 2H, NH_2), 7.20-7.60 (*m*, 5H, aromatic H); IR: 2750 (OH), 1650 (C = O) cm^{-1}.

Reaction of **13** *with hydrazine: Formation of 2,4-diamino-2-methyl pentane* (**14**)

A solution of **13** (0.05 mol) in *n*-propanol containing hydrazine hydrate (5 ml) was refluxed for 4-5 hr. The solvent was distilled off and the semi-solid residue triturated with chloroform. The chloroform extract on distillation gave **14** (250 mg, 40%) as a liquid. The solid residue was crystallised from ethanol to give triaminoguanidine hydriodide, m.p. 233° (lit.[5], 235°), identical (CO-IR) with an authentic sample.

Reaction of **7** *(R = H/Ph),* **8** *(R = CH_3/Ph) or* **13** *(R = CH_3/Ph) with thiourea (Table 1)*

A solution of pyrimidine derivative (0.05 mol) in

ethanol or DMF containing sodium ethoxide (0.15 mol) or HCl (0.1 ml) and thiourea (0.015 mol) was refluxed. The progress of reaction in each case was monitored by TLC. After the completion of the reaction, it was diluted with water, extracted with chloroform and the extract dried (Na_2SO_4). After distillation of the chloroform from the extract, **8** (R = H) was obtained, which crystallised from ethanol.

Acknowledgement

We thank the CSIR, New Delhi for financial assistance and Prof. P J Scheuer, University of Hawaii for the mass spectra.

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Esterification of Maleanilic Acids: Intramolecular Esterification Through Imidate Ester

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Maleanilic acids are easily esterified at room temperature with an abs. alcohol in the presence of thionyl chloride. It has been shown to proceed through an intramolecular migration of alkyl group of the intermediate imidate ester.

The esterification in general and of maleanilic acids in particular has been the subject of some recent reports[1-3]. In view of our latest report[4] about the facile esterification by mixing the acids with abs. alcohol and required amount of thionyl chloride at room temperature we used this method for the esterification of maleanilic acids, as we needed the esters in a synthetic sequence.

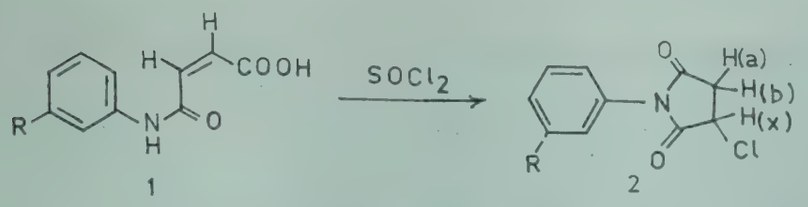
Maleanilic acids (**1a-e**; Table 1) underwent an exothermic reaction with thionyl chloride and the reaction mixture when poured in water or alcohol, gave the products **2a-e** (Table 1). Among these the structure of **2a** (m.p. 115°; lit.[5] m.p. 117°) is known (though not prepared by this method). The structure **2** was further confirmed by the mass (M^+ 225/223 abundance ratio 1 : 3 and other fragments) and PMR (a typical *ABX* pattern) spectra of **2b**.

Having failed to esterify maleanilic acids by this procedure it was thought that if an excess of a stronger nucleophile is available *in situ*, the reaction course might change. This prompted us to dissolve maleanilic acid **1a** in abs. ethanol, to which required amount of thionyl chloride was added. This reaction after standing overnight and work-up gave the desired ester **3a** (m.p. 104°) whose elemental analysis and PMR data (*t* at δ 1.3 for CH_3 and *q* at 4.35 for CH_2 protons in addition to other signals present in **1a**) were in agreement with the assigned structure.

This method was, therefore, used for the preparation of other alkyl esters (**3b-h**; Table 2) using appropriate abs. alcohols. All the alkyl esters showed characteristic signals in their PMR spectra for the ester alkyl protons. The yield of the ester was much lower in the case of isopropanol and the reaction did not take place with *t*-butanol. The insolubility of maleanilic acids **1d** and **1e** in alcohols, however, did not hinder their esterification, as on standing (under the experimental conditions) the complete dissolution of the insoluble acid indicated the completion of the reaction (ester being more soluble).

Table 1—Characterization Data of Maleanilic Acids (**1**) and Their Reaction Products (**2**) with Thionyl Chloride

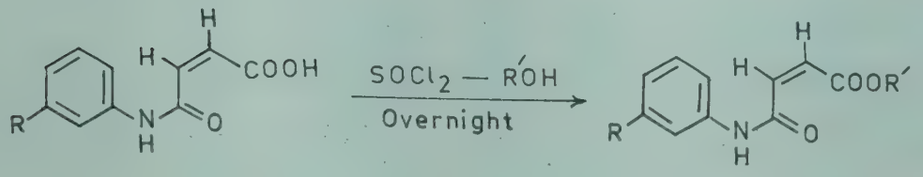
Compd	R	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)		
					C	H	N
1a	$-H$	201	95	$C_{10}H_9NO_3$	62.5 (62.8	4.8 4.7	7.1 7.3)
1b	$-CH_3$	170	98	$C_{11}H_{11}NO_3$	64.2 (64.4	5.2 5.4	6.9 6.8)
1c	$-OCH_3$	160	85	$C_{11}H_{11}NO_4$	—	—	—
1d	$-Cl$	185	85	$C_{10}H_8NO_3Cl$	53.3 (53.2	3.5 3.6	6.2 6.2)
1e	$-NO_2$	201	70	$C_{10}H_8N_2O_5$	—	—	—
2a	$-H$	115	75	$C_{10}H_8NO_2Cl$	57.2 (57.3	3.8 3.4	6.6 6.7)
2b	$-CH_3$	138	80	$C_{11}H_{10}NO_2Cl$	58.0 (59.1	4.4 4.5	6.5 6.6)
2c	$-OCH_3$	—	60	$C_{11}H_{10}NO_3Cl$	—	—	—
2d	$-Cl$	104	70	$C_{10}H_7NO_2Cl_2$	49.3 (49.2	2.8 2.9	5.8 5.7)
2e	$-NO_2$	186	65	$C_{10}H_7N_2O_4Cl$	—	—	—



1 2

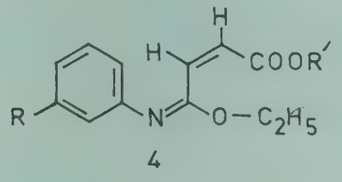
a. R = –H b. R = –CH_3 c. R = –OCH_3

d. R = –Cl e. R = –NO_2



1 3

	R	R′		R	R′
3a	–H	–C_2H_5	3e	–Cl	–CH_3
3b	–CH_3	–C_2H_5	3f	–Cl	–C_2H_5
3c	–CH_3	i–C_3H_7	3g	–Cl	n–C_3H_7
3d	–OCH_3	–C_2H_5	3h	–NO_2	–C_2H_5



4

a. R = –CH_3, R′ = –H

b. R = –CH_3, R′ = –CH_3

c. R = –H, R′ = –H

d. R = –Cl, R′ = –H

The esterification reaction of compound **1b**, when quenched with water after two and a half hours, gave a compound (m.p. 77°) in a quantitative yield. The PMR spectrum of this compound showed signals due to ethyl protons (3H *t*, δ1.3 and 2H *q*4.3) and an upfield shift of the doublet of doublets for the olefinic protons to δ 6.25 (in the case of **1b** or **3b** this signal was centered at δ 6.8). There was no signal for the D_2O exchangeable proton of –NH– group at δ 9.45 (present in **1b** and **3b**) but a signal due to exchangeable carboxylic proton appeared at 11.15. The IR (KBr) spectrum also showed the absence of –NH– group and the presence of carboxylic function. Based on these results and elemental analysis structure **4a** (Table 2) was assigned to this product. This structure would also explain the upfield shift for the olefinic protons of maleanilic acid **1b**.

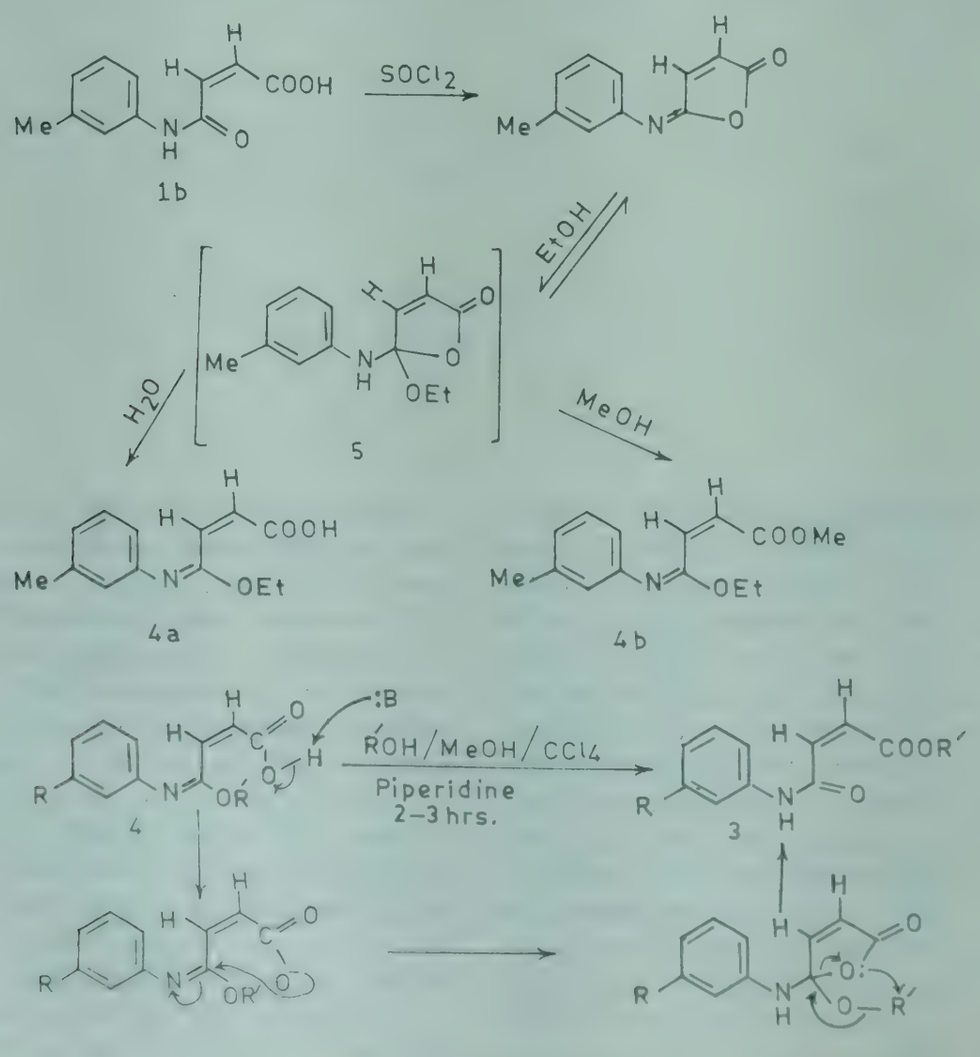
Compound **4a** could not be converted into ester **3b** under the experimental conditions or when allowed to stand under acidic conditions, or refluxed as such in CCl_4. However, when a solution of **4a** in abs. ethanol was treated with a drop of piperidine, the ester **3b** was obtained in a quantitative yield. Treatment of a solution of **4a** in CCl_4 or abs. methanol with a drop of piperidine also gave **3b** in quantitative yields irrespective of the alcohol or any other solvent used.

These experiments clearly indicate that the esterification involved intramolecular transfer of ethyl (alkyl) group of the imidate ester function to the carboxyl group. These facts led us to propose Scheme 1 for the esterification of maleanilic acids.

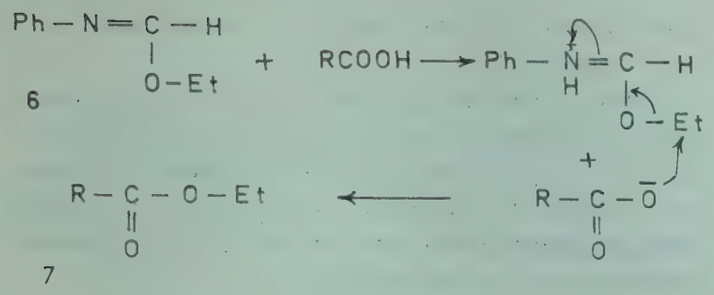
When the esterification reaction of **1b** was quenched with abs. methanol, compound **4b** (Table 2) was obtained whose PMR spectrum showed in addition to

Table 2—Characterization Data of Maleanilic Esters (3) and Their Derivatives

Compd	R	R′	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)		
						C	H	N
3a	$-H$	$-C_2H_5$	104	68	$C_{12}H_{13}NO_3$	65.5 (65.8	5.5 5.9	6.0 6.4)
3b	$-CH_3$	$-C_2H_5$	120	71	$C_{13}H_{15}NO_3$	66.9 (67.0	6.4 6.4	5.9 6.0)
3c	$-CH_3$	$i-C_3H_7$	138	52	$C_{14}H_{17}NO_3$	67.9 (68.0	6.6 6.9	5.5 5.7)
3d	$-OCH_3$	$-C_2H_5$	114	64	$C_{13}H_{15}NO_4$	—	—	—
3e	$-Cl$	$-CH_3$	154	65	$C_{11}H_{10}NO_3Cl$	—	—	—
3f	$-Cl$	$-C_2H_5$	152	72	$C_{12}H_{12}NO_3Cl$	56.9 (56.8	5.0 4.7	5.8 5.5)
3g	$-Cl$	$n-C_3H_7$	146	63	$C_{13}H_{14}NO_3Cl$	58.4 (58.3	5.3 5.2	5.2 5.2)
3h	$-NO_2$	$-C_2H_5$	154	62	$C_{12}H_{12}N_2O_5$	—	—	—
4a	$-CH_3$	$-H$	77	90	$C_{13}H_{15}NO_3$	66.5 (67.0	6.4 6.5	5.9 6.0)
4b	$-CH_3$	$-CH_3$	58	45	$C_{14}H_{17}NO_3$	68.1 (68.0	6.7 6.9	5.7 5.7)
4c	$-H$	$-H$	59	70	$C_{12}H_{13}NO_3$	—	—	—
4d	$-Cl$	$-H$	51	62	$C_{12}H_{12}NO_3Cl$	—	—	—



SCHEME 1



6

7

the signals of **4a**, a singlet due to CH_3 protons of methyl ester at δ 3.98 and the disappearance of the carboxylic proton at δ 11.15.

Thus, it appears that an intermediate of the type **5** is probably present in the reaction mixture, because when it is quenched with water, it gives **4a**, but when quenched with abs. methanol, **4b** is obtained. This is in agreement with the general reaction of isoimides[6]. The imidate ester of type **4a**, in the case of other maleanilic acids were also isolated and converted into the corresponding carboxylic esters (Table 2).

To further support this mechanism, the imidate ester **6** was prepared[7]. Compound **6**, when heated with aliphatic acids like acetic and propionic, gave the corresponding ethyl esters (**7**), which could be distilled out of the reaction mixture. The structure of these esters were confirmed by their PMR spectra.

Thus, it appears that imidate ester may act as a good reagent for the esterification of carboxylic acids.

Experimental Procedure

Melting points were taken in a conc. sulphuric acid-bath and are uncorrected. IR spectra were recorded on an SP 1200 spectrophotometer (ν_{max} in cm^{-1}) and 90 MHz PMR spectra on an EM-390 spectrometer (chemical shifts in δ, ppm).

The maleanilic acids were prepared by stirring equimolar quantities of amines and maleic anhydride in benzene at room temperature for 30 min and recrystallised from methanol.

Reaction of maleanilic acids (**1a-e**) *with thionyl chloride*: *Formation of compound* **2a-e**

A typical procedure is described below:

To maleanilic acid **1a** (1.91 g; 0.01 mol) was added thionyl chloride (4 ml) just to dissolve the former. The reaction flask was placed aside till the exothermic reaction ceased and a clear solution was obtained. It was poured into ice-water in installments with constant stirring. The resultant solid was filtered, washed with water, dried and recrystallised from methanol to give **2a** (1.5 g) m.p. 115° (lit.[5] m.p. 117°); IR (KBr): 1730 and 1220; PMR ($CDCl_3$): 7.4 (5H, *m*, Ar-H), 4.75 (1H, *q*, H_x), 3.3 (2H, *o*, H_a and H_b). The mass spectrum of **2b** showed peaks at *m/z* 225 (34%), 223 (100%) and 133 (91%).

Esterification of maleanilic acids (**1a-e**)

A typical procedure is described below:

To a sulution of maleanilic acid **1b** (2.05 g; 0.01 mol) in dry ethanol (10 ml) was added thionyl chloride (1.5 mol proportions) dropwise with occasional shaking. The reaction mixture was allowed to stand overnight under dry conditions, poured into ice-water and extracted with ether. The extract was washed successively with water, sodium bicarbonate solution, 1% HCl and water, dried (anhyd. Na_2SO_4), ether distilled and the solid recrystallised from ethanol to give **3b** (1.5 g) m.p. 120°, IR (KBr): 3330, 1720, 1690 and 1650; PMR ($CDCl_3$): 8.55 (1H, *s*, $-NH$, exchangeable with D_2O), 7.5 (4H, *m*, Ar-*H*), 7.1 (2H, *dd*, HC=CH), 2.35 (3H, *s*, $-CH_3$), 4.3 (2H, *q*, $-CH_2-$), and 1.3 (3H, *t*, $-CH_3$); MS: *m/z* 233, 107 and 159.

Only the starting maleanilic acid **1b** was isolated when *t*-butanol was used for esterification.

Preparation of compound **4a**

To the maleanilic acid **1b** (2.0 g; 0.01 mol) in dry ethanol (10 ml) was added thionyl chloride (1.5 mol proportions) dropwise with occasional shaking. The reaction mixture was allowed to stand for 2.5 hr under dry conditions, poured into ice-water with constant stirring and the precipitated solid filtered, washed with water dried and recrystallised from benzene-pet. ether to give **4a** (1.8 g), m.p. 77°; IR (KBr): 3400-3180, 1730, 1670 and 1640; PMR (CCl_4): 11.15 (1H, *s*, $-OH$), 7.2 (4H, *m*, Ar-*H*), 6.25 (2H, *dd*, HC=CH), 4.3 (2H, *q*, $-CH_2-$), 1.3 (3H, *t*, $-CH_3$) and 2.35 (3H, *s*, $-CH_3$).

Preparation of compound **4b**

To the maleanilic acid **1b** (2.0 g, 0.01 mol) in dry ethanol (10 ml) was added thionyl chloride (1.5 mol proportions) dropwise with occasional shaking, and the reaction mixture allowed to stand for 2.5 hr under dry conditions, poured into abs. methanol (5-6 ml), allowed to stand for about 2-3 hr and worked-up as in esterifcation experiments. The oily mass so obtained crystallised in 5-6 days on standing. The crystals were filtered, washed with cold chloroform and dried to give **4b** (0.75 g) m.p. 58°; PMR ($CDCl_3$): 7.35 (4H, *m*, Ar-*H*), 6.4 (2H, *dd*, HC=CH), 3.89 (3H, *s*, $-CH_3$ of methyl ester), 4.37 (2H, *q*, $-CH_2-$), 1.35 (3H, *t*, $-CH_3$) and 2.4 (3H, *s*, tolyl $-CH_3$); MS: *m/z* 233, 188, 107, 85, 59 and other characteristic fragments.

Conversion of compound **4a** *into ester* **3b**

(a) To a solution of **4a** (1 g) in abs. alcohol (10 ml) two drops of piperidine were added and the solution was allowed to stand for 3hr and worked-up as above to give **3b** (0.8 g); m.p. 120°, m.m.p. 119-20°.

(b) To a solution of **4a** (1 g) in CCl_4 (10 ml) were added two drops of piperidine and the reaction mixtrue was allowed to stand for 3hr and worked-up to give **3b** (0.83 g) m.p. 120°, m.m.p. 119-20°.

(c) The ethyl ester **3b** was also obtained by substituting abs. methanol for CCl_4 and keeping other conditions the same as above.

Compound **4a** could not be converted into **3b** under the following conditions:

(i) Refluxing of **4a** with either CCl_4 or abs. alcohol alone.

(ii) Treatment of **4a** with thionyl chloride in abs. alcohol overnight. In this case some oil was isolated which could not be identified.

(iii) Treatment of **4a** in ethanol containing a few drops of conc. sulphuric acid for 3 hr at room temperature.

Esterification of acetic and propionic acids with compound **6**

The acid to be esterified was mixed with an excess of compound **6** and the reaction mixture refluxed for half an hour and distilled to recover the alcohol formed. The distillation temperature was then raised and the resultant ester (ethyl acetate or ethyl propionate) distilled out at its boiling point.

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Synthesis & Reactions of 4,6,7,8-Tetrahydro-5(1*H*)-cinnolinones†‡

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Phenacyldimedone, acetonyldimedone and analogues of general structure **1** undergo reaction with hydrazine, alkylhydrazine and phenyl- and 4-nitrophenyl-hydrazines to form 4,6,7,8-tetrahydro-5(1*H*)-cinnolinones (**2**) while **1b** and 2,4-dinitrophenylhydrazine afford the perhydroindole **4b**. Tetrahydrocinnolinones **2a**, **2e** and **2f** yield the partially aromatised oximes **7a-c**, while the keto acid **13** gives the decarboxylated oxime **14** or the acylnitrone **15**. 1-Aminoalkyl- and 1-alkylcinnolinones (**2b-d** and **2g**) form the same oxime **7a** with concomitant loss of the 1-substituent presumably through a quaternary salt of the type **9**. 1,3-Diphenylcinnolinone **2b** is transformed under identical conditions to the quaternary salt **10a** in addition to two other products **11** and **12**. The oximes **7a-c**, **14** and the nitrone **15** on treatment with PPA do not yield the ring enlarged Beckmann products, but undergo Semmler-Wolff aromatisation to afford 5-aminocinnolines (**19a-d** and **20**). Compound **19a** is also formed from **7a** with conc. sulphuric acid or pyridine-phosphorous oxychloride and from 7,8-dihydro-5(1*H*)-cinnolinone (**16**) by a Schmidt reaction. Structures **19a-d** have been established by deaminating **19c** to known 3-phenylcinnoline and by the formation of pyrazolocinnoline **22** from the diazotisation of **19b**. While a number of interesting products are obtained from the oxime **7a** with a variety of acidic reagents, only phosphorous pentachloride transforms it to the expected pyridazinoazepinone **30**. The study has led to a number of unexpected reactions which have been rationalised.

Phenacyldimedone and analogues of the general structure **1** have not only great utility in the synthesis of heterocycles but also undergo unexpected reactions[1]. Reactions of **1a** with primary amines like anilines afford 1-arylperhydroindoles exhibiting antiimplantation activity[2], while with 1-aminopiperidine and N,N-disubstituted hydrazines, 3-aminoperhydroindoles[3,4] are produced. Hydrazine and some monosubstituted hydrazines afford 4,6,7,8-tetrahydro-5(1*H*)-cinnolinones of the type **2**, some of which have CNS depressant activity[5]. In a preliminary communication[6], we have commented on the unexpected formation of the oxime **7a** from **2a** and its unusual conversion into the aminocinnoline **19a** under Beckmann transformation conditions. Subsequently, we extended our study on the formation of cinnolines from **2** to nitrophenylhydrazines and investigated in some depth the origin of oximes **7** from **2** and their fate under a variety of acidic conditions. The results are presented in this paper.

Formation of 4,6,7,8-*tetrahydro*-5(1*H*)-*cinnolinones*

In an earlier paper[5], we have published several examples wherein R – R_3 were extensively varied, with R_3 being mostly H or aminoalkyl group. We have not studied the reaction of **1a** and **1b** with phenyl, 4-nitrophenyl- and 2,4-dinitrophenyl-hydrazines. The reaction of phenylhydrazine with **1a** gave rise to the cinnolinone **2b**. In the PMR spectrum of this product, the protons at C-6 and C-8 appeared as singlets at δ 2.21 and 2.31 respectively. On the other hand, in the PMR spectrum of the cinnolinone **2i**, obtained from **1d** and phenylhydrazine, the pairs of protons at C-6 (δ 2.19, 2.41) and C-8 (δ 1.99, 2.52) became nonequivalent because of the substituent at C-4. Since the phenyl group at C-1 can be expected to have a greater shielding effect on the protons at C-8 than on the ones at C-6, the proposed assignment is more realistic than a transposed one. The reaction of **1b** with 4-nitrophenylhydrazine gave rise to two products with m.p.s 108-10° and 295-98°. The former, $C_{17}H_{19}N_3O_3$, was clearly the expected cinnolinone **2j** which showed a two-proton singlet for C-4 methylene protons at δ 3.00 in its PMR spectrum. The latter product, $C_{34}H_{38}N_6O_6$($M^{+\cdot}-1$ at *m/z* 625) appeared to consist of two monomeric units, one being the cinnolinone **2j**; but instead of a two-proton singlet for C_4-H_2 at δ 3.00, two singlets were observed at 5.13 and 5.42, integrating for only one proton. Further, the indole unit **4a** also seemed to be present as evident from a high-field multiplet for two protons at C-2‴ and C-6‴ at δ 6.38 (see below), a singlet for one proton at C-3, and two broad singlets at 10.02 and 10.04 together integrating for one proton (NH). Considering that the CH_2 group at position-4 in **2j** will be activated for addition of a C=O group, we wish to formulate the dimeric product tentatively as a diastereoisomeric mixture of **3**, arising by reaction of **4a** with **2j**.

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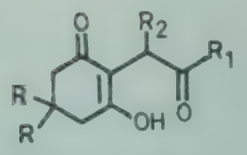
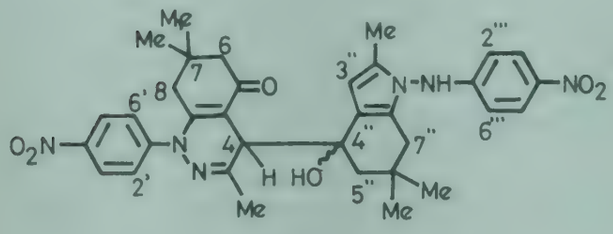


1 a R = CH_3 ; R_1 = Ph , R_2 = H
b R = R_1 = CH_3 ; R_2 = H
c R = R_2 = H ; R_1 = Ph
d R = R_2 = CH_3 ; R_1 = Ph



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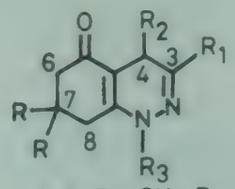


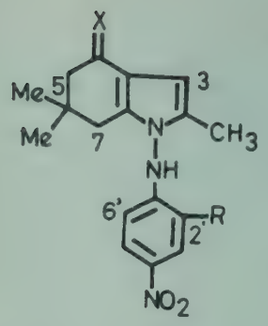
2 a R = CH_3; R_1 = Ph ; R_2 = R_3 = H
b R = CH_3 ; R_1 = Ph ; R_2 = H ; R_3 = $(CH_2)_2NMe_2$
c R = CH_3 ; R_1 = Ph ; R_2 = H ; R_3 = $(CH_2)_2NEt_2$
d R = CH_3 , R_1 = Ph , R_2 = H , R_3 = $(CH_2)_3NMe_2$
e R = R_1 = CH_3 ; R_2 = R_3 = H
f R = R_2 = R_3 = H ; R_1 = Ph
g R = R_3 = CH_3 ; R_1 = Ph ; R_2 = H
h R = CH_3 , R_1 = R_3 = Ph , R_2 = H
i R = R_2 = CH_3 ; R_1 = R_3 = Ph
j R = R_1 = CH_3 ; R_2 = H ; R_3 = 4-$NO_2C_6H_4$
k R = R_1 = CH_3 ; R_2 = CH_2CO_2H ; R_3 = H
l R = R_1 = CH_3 ; R_2 = CH_2CO_2Et ; R_3 = H

Unfortunately the high-field signals in the PMR spectrum of **3** were not amenable to incisive analysis. 2,4-Dinitrophenylhydrazine and **1b** again gave rise to two products with m.ps 210-12° and 270-72°. The former, $C_{17}H_{18}N_4O_5$, was not a cinnoline and was recognized readily to be the indole **4b**, the PMR spectrum of which exhibited a singlet for C_3-H at δ 6.40, a singlet for NH at 10.12 and a doublet for C-6′ proton at 6.33. An interesting observation in the spectrum was the splitting of protons at C-7 into an *AB* quartet, apparently due to differential shielding by the dinitrophenyl group held orthogonally (perhaps in a rigid ring by hydrogen bonding of the 2′-NO_2 group with the NH proton). The higher melting product from this reaction was identified as the 2,4-dinitrophenylhydrazone (**4c**) and **4b**. An alternative structure for **4c** would have been **5b** which was prepared unambiguously by acid-induced cyclization of **1b** to furan **5a** followed by reaction with 2,4-dinitrophenylhydrazine. In the event, **4c** was found to be different from **5b**. In contrast to **1b**, 2-phenacylcyclohexanone (**6a**) reacted with 2,4-dinitrophenylhydrazine to give only the bis-hydrazone **6b**.

Oximation studies on 4,6,7,8-*tetrahydro-5*(1*H*)-*cinnolinones*

Reaction of the cinnolinone **2a** with two moles of hydroxylamine hydrochloride in pyridine at 100° for several hours gave in about 95% yield, the oxime **7a** ($M^{+\cdot}$ at *m/z* 267) rather than the expected one (M 269). The aromatisation of the dihydropyridazine ring was inferred from the disappearance of the two-proton singlet around δ 3.0 ($C_4 - H_2$) in **2a** and the appearance of a singlet at 8.28 due to $C_4 - H$ in **7a**; singlets due to protons at C-6 and C-8 also experienced a downfield shift. The cinnolinones **2e** and **2f** gave rise to similar aromatised oximes **7b** and **7c** respectively in high yields. Reaction of **2a** with methoxylamine also led to the formation of the aromatised methoxime. Treatment of **7a** with toluenesulphonyl chloride in pyridine merely led to O-sulphonation and not to the expected Beckmann transformation product. Hydrolysis of **7a** with dil. sulphuric acid gave the ketone **16** in a low yield. This ketone was obtained in a better yield by treatment of **2a** with either methane- or *p*-toluene-sulphonyl chloride in pyridine. Exposure of **2a** to hot pyridine also led to the formation of **16** but in only 10% yield, rest of the starting material being recovered. Hence, a spontaneous aerial oxidation of **2a** to **16** could be ruled out as a sole prior step to the formation of **7a**, leaving hydroxylamine responsible for much of the aromatisation reaction. In occasional runs of **7a**, the PMR as well as mass spectra of the crude product showed the presence of **16**. Thus, oxidation of **2a** to **16** by hydroxylamine followed by further reaction with excess hydroxylamine may be a major route for the formation of **7a**.

Another interesting observation in the oximation studies was the transformation of 1-methyl(**2g**)- and 1-aminoalkyl(**2b-2d**)-cinnolinones into the same oxime **7a** in moderate yields by reaction with excess hydroxylamine hydrochloride in pyridine. It was readily ascertained that the 1-methyl derivative (**2g**) was totally resistant to aerial oxidation in hot pyridine. Hence, in these cases it was likely that 1-alkylquaternary salts of **7a** were formed which suffered



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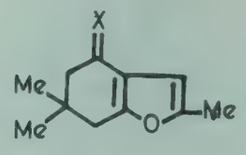
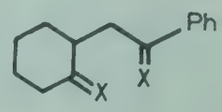
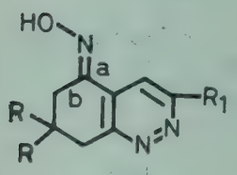
b R = NO_2 ; X = O
c R = NO_2 ; X = 2,4-diNO_2-C_6H_3NHN



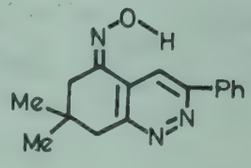
5 a X = O
b X = 2,4-diNO_2-C_6H_3NHN



6 a X = O
b X = 2,4-diNO_2-C_6H_3NHN



7 a R = CH_3, R_1 = Ph
b R = R_1 = CH_3
c R = H, R_1 = Ph



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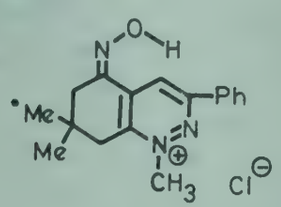

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dealkylation. This was demonstrated by carrying out the reaction of **2g** with an equimolar quantity of hydroxylamine hydrochloride in pyridine. The product mixture contained not only oxime **7a** and ketone **16**, but also the quaternary chloride **9** (PMR: N_1-CH_3 at δ 4.63 and C_4-H at 8.93; $M^{+\cdot}$ at *m/z* 281 for betaine). That the oxidation process was at least partly radical-induced, became evident during the oximation of the 1,3-diphenylcinnolinone (**2h**) with excess hydroxylamine hydrochloride. The product mixture contained besides the 1-phenylquaternary salt **10a**, small quantities of 1,3,4-triphenylcinnolinone oxime (**11**) and 1-unsubstituted 4-hydroxycinnolinone (**12**). Structures of these products are based on elemental analyses and mass and PMR spectral data, especially PMR (**11**: signals for protons of three phenyl groups, singlet for C_4-H at δ 5.55; **12**: signals for protons of one phenyl group, singlet for C_4-H at δ 6.91).

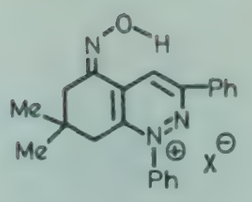
Lastly, we studied the oximation of cinnolinone resulting from the triketo acid **13**. This on reaction with excess hydrazine hydrate in ethanol suffered decarboxylation and gave the cinnolinone **2k** as an oil which without purification was treated with hydroxylamine to afford the oxime **14**. On the other hand, **2k** could be esterified with ethanol to give the cinnolinone **21** which afforded the tricyclic system **15** with hydrazine. The structure of **15** is based on elemental analysis and mass spectrum. In the mass spectrum, there was a prominent (M − 16) peak as would be expected by the presence of a nitrone group. The PMR spectrum of **15** could be run only in trifluoroacetic acid and indicated that in this solvent it existed completely in the enolic form (**15b**) (singlet for =CH at δ 7.40; no signal for CH_2).

Intramolecular oxidation-reduction of ketocinnoline **2a** *to hydroxycinnoline* **18**

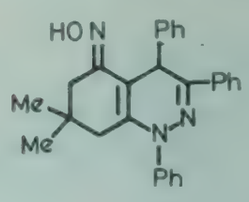
Treatment of **2a** in dioxane with dil. HCl under reflux transformed it into the isomeric alcohol **18** (yield 60%) which was also obtained from **16** by reduction with sodium borohydride. The formation of **18** from **2a** can be visualised to have occurred through the species **17** by a prototropic shift. The structure of **18** (IR: no C=O, but OH band) was specially supported by PMR data (singlet for C_4-H at δ 8.15, multiplet for C_5-H at 4.85 and nonequivalence of the two hydrogen atoms at C-6).

Behaviour of oxime **7a-c** *and* **14** *and pyridocinnolinone* **15** *towards PPA*

An attempted Beckmann rearrangement of **7a** with hot PPA resulted in the unexpected formation of **19a** in 70% yield by a Semmler-Wolff rearrangement[6]. The same transformation was brought about by hot conc. sulphuric acid or phosphorous oxychloride-pyridine in 85 and 40% yields respectively. Similar PPA-induced rearrangements occurred with **7b**, **7c** and **14** to afford induced **19b-d** in 95, 50 and 65% yields respectively. The product obtained by the action of PPA on **15** was not the expected lactam **21**, but it was the hydrolysis product **20** although the mass spectrum showed the



10 a X = Cl
b X = I



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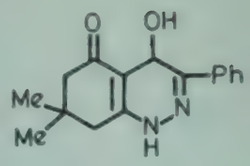

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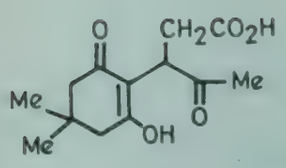

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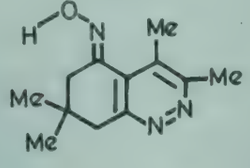

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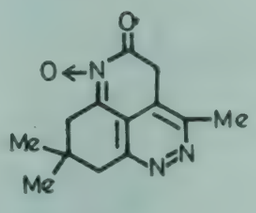
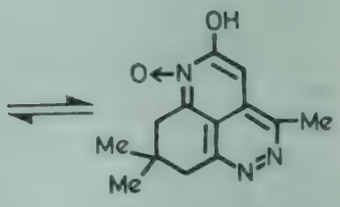
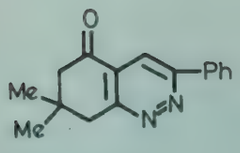


15a



15b



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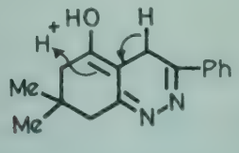

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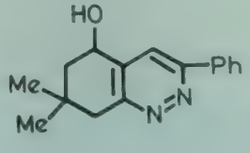

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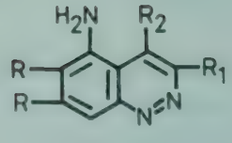
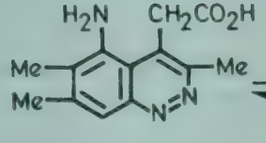
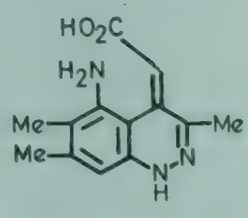


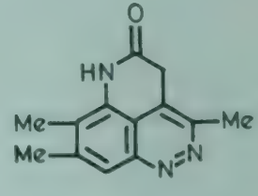
19a R = Me ; R_1 = Ph ; R_2 = H
b R = R_1 = Me , R_2 = H
c R = R_2 = H ; R_1 = Ph
d R = R_1 = R_2 = Me



20a



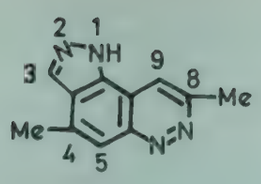
20b



21

molecular ion peak at *m/z* 227 corresponding to the cyclodehydration product **21**. Compound **20** was soluble in aq. sodium hydroxide and besides giving correct elemental analysis it exhibited typical bathochromic shifts in acidic medium compared to neutral solvent[6]. The PMR spectrum in DMSO-d_6 displayed two singlets at δ 5.45 and 6.40. We wish to propose tentatively that **20** exists as a mixture of the tautomers **20a** and **20b** and ascribe the two signals respectively to the vinylic proton in the former and the CH_2 protons in the latter. The amine **19b** was routinely transformed into chloracetyl (**25a**) and pyrrolidinoacetyl (**25b**) derivatives and **19a** into dicloracetyl **26** derivative for biological screening.

The structures of **19c-d** rested firmly on elemental analysis and UV, IR, mass and PMR spectral data, the last one being of the greatest diagnostic significance. Thus, in the PMR spectrum of **19**, the singlets due to protons at C-6 and C-8 observed for **7a** at δ 2.67 and 3.05, disappeared to give rise to a singlet in the aromatic region at 7.60, while the two methyl groups appeared as downfield singlets at 2.33 and 2.47 from their original position at 1.07 in **7a**. Compound **19b** and even more so **19d** are the interesting examples of 5-aminocinnolines sprinkled liberally with methyl groups. Diazotisation-deamination of **19c** afforded 3-phenylcinnoline identical with a known sample. The marked upfield shift of C_4-proton in the latter



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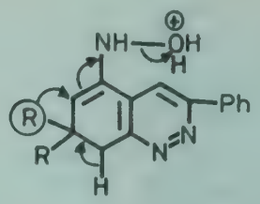

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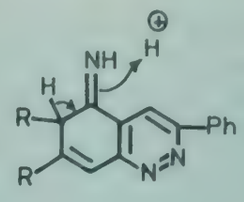

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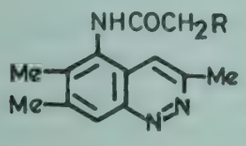
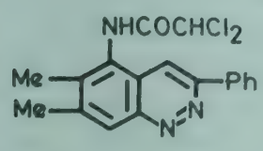


25a R = Cl

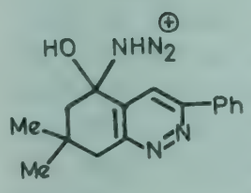
b R = Pyrrolidino



26

compared to the same proton in **19c** would be explicable on the basis of deshielding influence of the amino group at position-5 in **19c**. A similar reaction performed on **19b** did not lead to deamination. Instead pyrozole **22** was formed indicating that one of the methyl groups which had migrated in the rearrangement of **7b** had wandered to position-6 rather than 8 resulting in the formation of **19b** and not its 7,8-dimethyl isomer. Pyrazole formation in this reaction was unexpected but not entirely unprecedented, since the diazotisation of 3-aminolepidine has been reported to yield a pyrozoloquinoline[8].

From a comparison of the chemical shifts for C_4-H proton in ketone **16** (δ 8.22) and oxime **7a** (δ 8.28), we have concluded that the latter has *E*- rather than *Z*-configuration (**8**). In a few other oxime the N−OH bond is tilted towards the pyridazine ring as in **9** (probably) (C_4-H δ 8.93), **10a** (C_4-H δ 9.20) and **36** (certainly) (C_4-H, δ9.33).A Beckmann rearrangement of **7a** would required bond-a attached to the electron-poor pyridazine ring to migrate. We have proposed[6] that this is probably a more energy-demanding process than the Semmler-Wolff aromatisation for which many mechanisms differing only in details have been proposed[9,10]. We feel that oxime **7a** may exist in equilibrium with species **23** (protonated form), wherein the loss of a water molecule would trigger loss of a proton from position-8 followed by migration of methyl group to C-6. Imine **24** thus arising would tautomerise to the aminocinnoline **19a**. Oximes of heterocyclic ketones such as 5-keto-5,6,7,8-tetrahydroquinoline have been shown recently to undergo facile Semmler-Wolff rearrangement[11–17]. Parallels to the transformation **15**→**21** have also been reported very recently in quinoline series[18–20].



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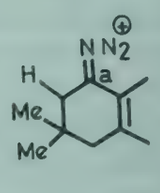

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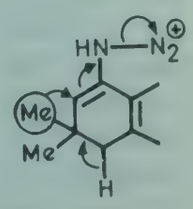

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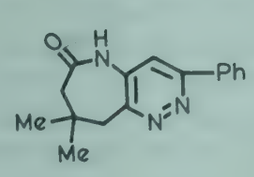

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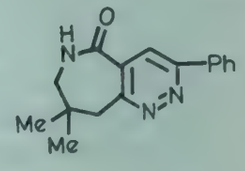


31

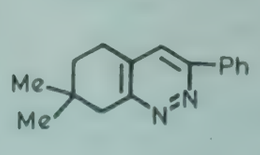
Attempted Schmidt reaction on ketone **16**

Ketone **16** was inert towards sodium azide and trifluoroacetic acid—anhydride mixture, but in the presence of conc. sulphuric acid conversion to **19a** occurred in 75% yield. The reaction can be envisaged to proceed through the standard intermediate species **27** and **28** (configuration of $=NH_2^{(+)}$ assumed to be the one shown). The reluctance again of the electron-deficient bond-a in **28** to migrate nudges the molecule to tautomerise to **29** which by the loss of nitrogen goes over to species **24** and thence inevitably to amine **19a**. At the time of our preliminary disclosure[6], this was the only recorded abnormal Schmidt rearrangement, the recalcitrancy being traceable to the attachment of the ketone to the electron-deficient pyridazine ring. Latter, some 5-oxo-5,6,7,8-tetrahydroquinolines were also reported to be transformed partly into 5-aminoquinolines and partly into pyridoazepines under the Schmidt reaction conditions[12].

Behaviour of oxime **7a** *towards other acidic reagents*

The transformation of **7a** into **19a** by PPA, conc. sulphuric acid or phosphorous oxychloride-pyridine has been already recorded as also its hydrolysis to ketone **16** with hot dil. sulphuric acid. Several other reagents were tried. Phosphorous pentachloride was uniquely able to bring about the much-sought-after rearrangement to the azepinone, although in unspectacular yield (11.5%). The *E*-configuration of the oxime **7a** should dictate the formation of **30** rather than **31**. The former was indeed the structure of the product, since the singlet due to C_4-H had moved upfield to δ 7.67 compared to its position in **7a** (δ 8.28).

Further the NH signal at δ 10.0 was only a singlet. Reaction of **7a** with formic acid gave a cumbersome mixture of four products which was separated into its components by fractional crystallization and chromatography. Two were known compounds, viz. **2a** formed by reductive hydrolysis and **16** by oxime cleavage. The third product was the dihydrodesoximino derivative **32** and the fourth, the product of reductive formylation, **33**. Structures **32** and **33** were firmly supported by mass and PMR spectral data. The PMR analysis of the total crude product revealed the composition of the mixture as: **2a** (10%), **16** (10%), **32** (50%) and **33** (30%). Finally the oxime **7a** was treated with hot 6 *N* hydrochloric acid in dioxane. The PMR analysis of the total crude product showed it to be a mixture of **7a** (10%), **16** (30%) and a new compound found to be the chloroketone **35** (60%) which on crystallization from ether followed by ethanol gave fairly pure **35a** in about 25% yield. The chloroketone **35a** was characterized by elemental analysis and mass (M^+ at *m/z* 286, 288) and PMR (C_6-H as singlet at δ 4.40) and nonequivalence of C_8-protons. The formation of **35a** can be visualized to have occurred by the addition of chloride ion to species **23** to afford **34** and subsequent hydrolysis. We considered an alternative possibility of hydroxylamine and hydrochloric acid reacting together to generate chlorine which can halogenate **16** to produce **35a**. The hydrolysis of **7a** with 6*N* hydrochloric acid was accordingly carried out in the presence of excess hydroxylamine hydrochloride and the product chromatographed over silica gel. Chloroketone **35a** was again obtained, but only in about 13% yield. A more polar product from the column analyzed for the molecular formula $C_{32}H_{31}N_5O_4$, although the mass spectrum did not show the molecular ion due to extensive decomposition. The PMR spectrum showed signals for four different tertiary methyl groups, a singlet due to CH $-$O, two different signals for the proton on the pyridazine ring, one of them being very low field (δ 9.33) and an oximino proton. These data could be best accommodated by the structural representation **36a** with unresolved ambiguity about the nature of R and R_1 and also regarding the stereochemistry of the carbon atoms involved in the ether linkage. The third and most polar product was tentatively considered to be **36b**, although the mass spectrum did not show the molecular ion to confirm the molecular formula. Products **36a** and **36b** probably arise by partial or complete oximation of the diketone corresponding to **36a**. The origin of this diketone can be traced to **35a** yielding the hydroxyketone **35b** which is further oxidised to a diketone and the two involving themselves in an intermolecular hemiketal formation. The oximino group in **36a** is deliberately oriented as shown, because of the occurrence of the signal for the concerned proton at C-4′ at a very low field (δ 9.33), compared to the other C_4-H (δ 8.42). Treatment of **7a** with acetic acid saturated with hydrogen chloride gas also gave chloroketone **35a** in 15% yield, the rest of the oxime being recovered. The formation of α-



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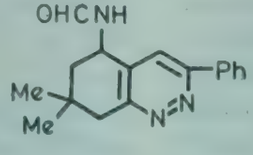

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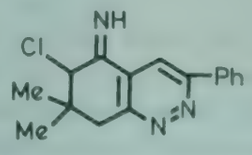

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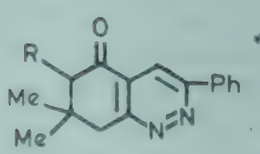
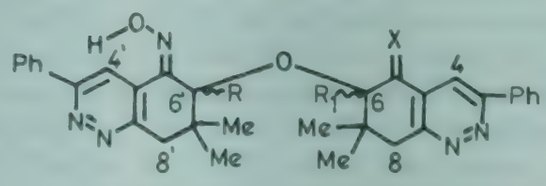


35 a R = Cl

b R = OH



36 a X = O, R = H, R_1 = OH or vice versa

b X = NOH, R = H, R_1 = OH

chlorotetralone from tetralone oxime using Beckmann's mixture has been reported[21].

Experimental Procedure

Formation of 4,6,7,8-*tetrahydro*-5-(1*H*)-*cinnolinones* (**2**)

Ketone **1a** (3.9 g), phenyl hydrazine (1.7 g) and ethanol (20 ml) were heated under reflux for 20 hr. The solution was evaporated and the residue triturated with hexane to give a solid which was crystallised from methylene chloride-hexane to afford **2h** (2.9 g), m.p. 131-33°; PMR ($CDCl_3$): δ 1.03 (*s*, 6H, $2\times CH_3$), 2.21 (*s*, 2H, C_6-H_2), 2.31 (*s*, 2H, C_8-H_2), 3.52 (*s*, 2H, C_4-H_2), 7.22-7.56 (*m*, 8H, Ar-*H*), 6.96-7.16 (*m*, 2H, Ar-*H*).

Ketone **1d** (0.7 g) and phenylhydrazine (0.35 g) were warmed in ethanol (3 ml). The solution was left at 28° for 24 hr and made acidic with 3*N* hydrochloric acid. The solid product was crystallised from ether-hexane to give **2i** (0.8 g), m.p. 156-60° (Found: C, 80.0; H, 7.2; N, 8.3. $C_{23}H_{24}N_2O$ requires C, 80.2; H, 7.0; N, 8.1%); $M^{+\cdot}$ at *m/z* 344; PMR ($CDCl_3$): δ 0.96 (*s*, 3H, CH_3), 1.08 (*s*, 3H, CH_3), 1.12 (*d*, $J=7$ Hz, 3H, C_4-CH_3), 1.99 (*d*, $J=17$ Hz, C_8-H), 2.19 (*d*, $J=16$ Hz, C_6-H), 2.41 (*d*, $J=16$ Hz, $C-H$), 2.52 (*d*, $J=17$ Hz, C_8-H), 4.44 (*q*, $J=7$ Hz, 1H, C_4-H), 7.22-7.56 (*m*, 8H, Ar-*H*), 7.78-8.04 (*m*, 2H, Ar-*H*).

Ketone **1b** (2.00 g) and 4-nitrophenylhydrazine (1.5 g) were heated under reflux for 20 hr and cooled. The precipitate was filtered off and the filtrate concentrated to remove a further crop. The final mother liquor deposited crystals which were recrystallized from ethanol to give **2j** (1 g), m.p. 108-10° (Found: C, 65.3; H, 6.3; N, 13.1. $C_{17}H_{19}N_3O_3$ requires C, 65.2; H, 6.1; N, 13.4%); $M^{+\cdot}$ at *m/z* 313; PMR ($CDCl_3$): δ 1.03 (*s*, 6H, $2\times CH_3$), 2.08 (*s*, 3H, C_3-CH_3), 2.30 (*s*, 4H, C_6-H_2 and C_8-H_2), 3.00 (*s*, 2H, C_4-H_2), 7.47 (*m*, 2H, C_2-H and $C_{6'}-H$), 8.27 (*m*, 2H, $C_{3'}-H$ and $C_{5'}-H$).

The ethanol-insoluble precipitate was **3** (1 g), m.p. 295-98° (Found: C, 64.7; H, 6.3; N, 13.8. $C_{34}H_{38}N_6O_6$ requires C, 65.2; H, 6.1; N, 13.4%); $(M^{+\cdot}-1)$ at *m/z* 625; PMR (DMSO-$CDCl_3$): δ 5.1, 5.4 (2*s*, together 1H, C_4-H), 6.38 (*m*, $C_{2'''}-H$ and $C_{6'''}-H$), 6.43 (*s*, 1H, $C_{3'''}-H$), 7.50-7.77 (*m*, 2H, Ar-*H*), 7.95-8.35 (*m*, 4H, Ar-*H*), 10.02, 10.04 (2*s*, together 1H, NH).

Ketone **1b** (1 g) in ethanol (10 ml) was added to a warm solution of 2,4-dinitrophenylhydrazine (1 g) in ethanol (50 ml) containing conc. hydrochloric acid (2 ml). After 16 hr at 28°, the red crystalline precipitate was filtered and washed with ethanol, yield 0.7 g. Recrystallisation from methylene chloride-methanol gave **4c** (0.5g), m.p. 270-72° (d) (Found: C, 50.9; H, 4.1; N, 20.2. $C_{23}H_{22}N_8O_8$ requires C, 51.3; H, 4.1; N, 20.8%); $M^{+\cdot}$ at *m/z* 538. The ethanol mother liquor from the above reaction slowly deposited a light orange solid which recrystallized from methylene chloride-ether to give **4b**; yield 0.7 g, m.p. 210-12° (Found: C, 57.3; H, 5.4; N, 15.7. $C_{17}H_{18}N_4O_5$ requires C, 57.0; H, 5.1; N, 15.6%); $M^{+\cdot}$ at *m/z* 358; PMR ($CDCl_3$): δ 1.07, 1.11 (2*s*, each 3H, $2\times CH_3$), 2.12 (*s*, 3H, C_2-CH_3), 2.29 (*d*, $J=16$ Hz, 1H, C_7-H), 2.36 (*s*, 2H, C_5-H_2), 2.64 (*d*, $J=16$ Hz, 1H, C_7-H), 6.33 (*d*, $J=9$ Hz, $C_{6'}-H$), 6.40 (*s*, 1H, C_3-H), 8.32 (*d*×*d*, $J=9$, 3 Hz, C_5-H), 9.15 (*d*, $J=3$ Hz, $C_{3'}-H$), 10.12 (*s*, 1H, NH). Treatment of ketone **4b** with 2,4-dinitrophenylhydrazine gave **4c**, m.p. and m.m.p. 270-72°.

This compound was different from the isomeric dinitrophenylhydrazone (**5b**) of furan **5a** which was made as follows: Ketone **1b** (1 g), ethanol (10ml) and conc. sulphuric acid (3drops) were heated under reflux for 22 hr. The solution was evaporated and the residue chromatographed over silica gel (50 g) using methylene chloride-hexane (3:1) as eluant. Furan **5a** was obtained in the first two fractions as a gum which slowly solidified, yield 0.8 g, m.p. 67-69°, $M^{+\cdot}$ at *m/z* 178; PMR ($CDCl_3$): δ 1.10 (*s*, 6H, $2\times CH_3$), 2.10 (*s*, 3H, C_2-CH_3), 2.13 (*s*, 2H, C_5-H_2), 2.65 (*s*, 2H, C_7-H_2), 6.20 (*s*, 1H, C_3-H); gave a dinitrophenylhydrazone (**5b**) m.p. 212-14°; m.m.p. with **4b** was depressed (Found: C, 56.9; H, 5.3; N, 15.3. $C_{17}H_{18}N_4O_5$ requires C, 57.0; H, 5.1; N, 15.6%).

2-Phenacylcyclohexanone **6a** (1 g) in ethanol (10 ml) was added to a warm solution of 2,4-dinitrophenylhydrazine (0.95 g) in ethanol (150 ml) and conc. hydrochloric acid (2 ml). After 72 hr at 28°, the red precipitate was filtered and recrystallized from methylene chloride-ether to give the bis-2,4-dinitrophenylhydrazone (**6b**) as orange crystals, yield 0.1 g, m.p. 250-53° (Found: C, 54.7; H, 4.3; N, 19.5. $C_{26}H_{24}N_8O_8$ requires C, 54.2; H, 4.2; N, 19.4%).

Oximation studies on 4,6,7,8-*tetrahydro*-5(1*H*)-*cinnolinones*

Cinnolinone **2a** (7.0 g) and hydroxylamine hydrochloride (3.8 g) were heated in pyridine (30 ml) on a water-bath for 16 hr. The resultant solution was diluted with water and the solid filtered and recrystallized from ethanol to give the oxime **7a** (6.9 g), m.p. 261-62° (Found: C, 71.7; H, 6.8; N, 15.4. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%); $M^{+\cdot}$ at *m/z* 267; PMR (DMSO-d_6 + $CDCl_3$): δ 1.07 (*s*, 6H, $2\times CH_3$), 2.67 (*s*, 2H, C_6-H_2), 3.05 (*s*, 2H, C_8-H_2), 7.35-7.70 (*m*, 3H, Ar-*H*), 7.90-8.20 (*m*, 2H, Ar-*H*), 8.28 (*s*, 1H, C_4-H), 11.92 (*s*, 1H, NOH). The same oxime was obtained in 15-50% yield when the cinnolines **2b-2d** were treated with hydroxylamine in a similar way. The product was isolated by extraction of the diluted

pyridine solution with ether, evaporation and crystallization of the residue from ethanol.

When **7a** was treated with *p*-toluenesulphonyl chloride in pyridine at 28° for 16 hr, it formed the O-tosyl derivative, m.p. 158-59° (Found: C, 65.5; H, 6.0; N, 10.1. $C_{23}H_{23}N_3O_3$ requires C, 65.5; H, 5.5; N, 10.0%); PMR ($CDCl_3$): δ 1.05 (*s*, 6H, $2\times CH_3$), 2.45 (*s*, 3H, Ar-C*H*$_3$), 2.73 (*s*, 2H, C_6-H_2), 3.10 (*s*, 2H, C_8-H_2), 7.35-8.15 (*m*, 9H, Ar-*H*), 8.15 (*s*, 1H, C_4-H).

Ketone **2a** (0.5 g), methoxylamine.HCl (0.35 g) and pyridine were heated at 100° overnight. The solution was poured into water and the product filtered and crystallized from ethanol to give the methoxime (0.4 g), m.p. 140-44° (Found: C, 72.4; H, 7.0; N, 14.9. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9%); PMR ($CDCl_3$): δ 1.03 (*s*, 6H, $2\times CH_3$), 2.55 (*s*, 2H, C_5-H_2), 3.02 (*s*, 2H, C_7-H_2), 4.03 (*s*, 3H, OCH_3), 7.30-7.65 (*m*, 3H, Ar-*H*), 7.95-8.20 (*m*, 2H, Ar-*H*), 8.25 (*s*, 1H, C_4-H).

Ketone **2e** (16.0 g) and hydroxylamine hydrochloride (12.0 g) when heated in pyridine (50 ml) at 100° for 16 hr gave the oxime **7b** (16 g), m.p. 260-61° (from methanol) (Found: C, 64.5; H, 7.6; N, 20.6. $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.4; N, 20.5%); PMR (DMSO-d_6 + $CDCl_3$): δ 1.00 (*s*, 6H, $2\times CH_3$), 2.57 (*s*, 2H, C_4-H_2),2.61 (*s*, 3H, C_3-CH_3), 2.94 (*s*, 2H, C_8-H_2), 7.72 (*s*, 1H, C_4-H), 11.85 (*s*, 1H, NOH).

Similarly **1c** gave the oxime **7c**, m.p. 280-82° (from methanol) (Found: C, 70.1; H, 5.6; N, 17.6;. $C_{14}H_{13}N_3O$ requires C, 70.3; H, 5.5; N, 17.6%); PMR (DMSO): δ 7.35-7.70 (*m*, 3H, Ar-*H*), 7.85-8.20 (*m*, 2H, Ar-*H*), 8.25 (*s*, 1H, C_4-H), 11.97 (*s*, 1H, NOH).

Ketoacid **13**[22] (2.55 g) was mixed with hydrazine hydrate (1 g) when an exothermic reaction took place. The mixture was diluted with ethanol (20ml), brought to reflux on a water-bath and set aside for ½ hr. The solution was concentrated to a small volume and treated with alcoholic HCl, when excess hydrazine separated out as hydrochloride, m.p. 207° (d). It was filtered off and the filtrate diluted with ether to give the oxocinnoline hydrochloride (**2k**, HCl) as a yellow oil (2 g). This salt was heated with hydroxylamine hydrochloride (1 g) and pyridine (10 ml) for 6 hr on a steam-bath. After removal of pyridine *in vacuo*, ice was added to give the oxime **14** (0.5 g), m.p. 243-45° (d) (from benzene-ethanol) (Found: C, 66.1; H, 8.0; N, 19.0. $C_{12}H_{17}N_3O$ requires C, 65.7; H, 7.8; N, 19.2%); PMR ($CDCl_3$ + DMSO-d_6): δ 1.03 (*s*, 6H, $2\times CH_3$), 2.57 (*s*, 3H, C_3-CH_3), 2.70 (*s*, 3H, C_4-CH_3), 2.70 (*s*, 2H, C_6-H_2), 2.93 (*s*, 2H, C_8-H_2), 10.85 (*s*, 1H, NOH).

Keto acid **13** (2.55 g) was treated with hydrazine hydrate (1 g) and left in ethanol (5 ml) at 28° for 16 hr. More ethanol (50 ml) and sulphuric acid (2 ml) were added and the solution again was left at 28° for 48 hr. The separated hydrazine sulphate was filtered off and the filtrate evaporated. The residue was treated with sodium bicarbonate and extracted with ether to give **2l** as an oil (2 g). It was heated with hydroxylamine hydrochloride (1.5 g) in pyridine (5 ml) at 100° for 16 hr to give 4,5,7,8-tetrahydro- 3,8,8-trimethyl 5-oxo-9*H*-pyrido[4,3,2-*de*]cinnoline-6-oxide (**15**) (0.75 g) (from ethanol); m.p. 285° (d) (Found: C, 64.0; H, 6.2; N, 17.1. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%); $M^{+\cdot}$ at *m/z* 245; PMR (CF_3CO_2H): δ 1.40 (*s*, 6H, $2\times CH_3$), 2.90 (*s*, 3H, C_3-CH_3), 3.35 (*s*, 2H, C_6-H_2), 3.53 (*s*, 2H, C_8-H_2), 7.40 (*s*, 1H, =CH).

Oximation of 4,6,7,8-*tetrahydro*-1,7,7-*trimethyl*-3-*phenyl*-5(1*H*)-*cinnolinone*

Ketone **2g** (2.7 g), hydroxylamine hydrochloride (0.75 g) and pyridine (25ml) were heated under reflux for 22 hr. The solvent was evaporated and the residual blackish gum washed with water. The aqueous washing was extracted with ether and the water layer evaporated to dryness. The residue was crystallised from ethanol-ether to give **9** (0.5 g), m.p. 239-40° (Found: C, 57.4; 57.4; H, 6.7; 6.6; N, 11.3; Cl, 13.3, 13.0. $C_{17}H_{20}ClN_3O.2H_2O$ requires C, 57.6; H, 6.8; N, 11.9; Cl, 10.0%); $M^{+\cdot}$ at *m/z* 281 (for betaine); PMR (DMSO-d_6): δ 1.10 (*s*, 6H, $2\times CH_3$), 2.53 (*s*, 2H, C_6-H_2), 2.67 (*s*, 2H, C_8-H_2), 4.63 (*s*, 3H, $N-CH_3$), 7.45-7.80 (*m*, 3H, Ar-*H*), 7.85-8.35 (*m*, 2H, Ar-*H*), 8.93 (*s*, 1H, C_4-H), 12.70 (*s*, 1H, NOH). The water-insoluble gum was triturated with ethanol to give the oxime **7a** (0.6 g), m.p. and m.m.p. 250°. Ketone **16** was present in the mother liquor as revealed by TLC and mass spectrometry. When the reaction between the ketone **2g** (0.8 g) and hydroxylamine hydrochloride (0.7 g) in pyridine (5 ml) was carried out on a steam-bath for 16 hr and the reaction mixture worked-up (evaporation and trituration with water), a gum was obtained which became crystalline with ether to afford the oxime **7a** (0.5 g), m.p. 253° (d).

Oximation of 4,6,7,8-*tetrahydro*-7,7-*dimethyl*-1,3-*diphenyl*-5(1*H*)-*cinnolinone*

A mixture of ketone **2h** (2.8 g), hydroxylamine hydrochloride (2 g) and pyridine (15 ml) was heated at 90° for 18 hr and the solvent removed. The residual gum was washed with a little water and then extracted with ether. The ether-insoluble residue (0.85 g) was recrystallised from methanol-ether to give **10a**, m.p. 261-63° (Found: C, 69.0; H, 6.3; N, 11.2; Cl, 11.2. $C_{22}H_{22}ClN_3O$ requires C, 69.6; H, 5.8; N, 11.2; Cl, 9.3%); $M^{+\cdot}$ at *m/z* 343 (for betaine); PMR (DMSO-d_6): δ 1.0 (*s*, 6H, $2\times CH_3$), 2.71 (*s*, 2H, C_6-H_2), 2.95 (*s*, 2H, C_8-H_2), 7.53-7.73 (*m*, 34, Ar-*H*), 7.81 (*s*, 5H, NC_6H_5), 8.00-8.27 (*m*, 2H, Ar-*H*), 9.30 (*s*, 1H, C_4-H), 12.95, (*s*, 1H, NOH). The chloride could be exchanged with iodide ion to provide the quaternary

iodide **10b**, m.p. 257-59° (from methanol-ether) (Found: C, 56.0; H, 5.0; N, 9.3. $C_{22}H_{22}IN_3O$ requires C, 56.1; H, 4.7; N, 8.9%); $M^{+\cdot}$ at *m/z* 343 (for beatine); PMR (DMSO-d_6): δ 1.00 (*s*, 6H, $2\times CH_3$), 2.72 (*s*, 2H, C_6-H_2), 2.96 (*s*, 2H, C_8-H_2), 7.53-7.76 (*m*, 3H, Ar-*H*), (*s*, 5H, NC_6H_5), 8.00-8.27 (*m*, 2H, Ar-*H*), 9.20 (*s*, 1H, C_4-H), 12.95 (*s*, 1H, NOH).

The ether-soluble part from the oximation was chromatographed over silica gel., elution of the column being done with chloroform. Approximately 25 ml fractions were collected. Fractions 1-4 eluted a yellow band from which **11** (50 mg) was obtained; m.p. 208-10° (from methylene chloride-hexane) (Found: C, 79.2; H, 6.9; N, 9.6. $C_{28}H_{27}N_3O$ requires C, 79.8; H, 6.5; N, 10.0%); $M^{+\cdot}$ at *m/z* 421; PMR (DMSO-d_6): δ 0.84, 0.89 (2*s*, 6H, $2\times CH_3$), 1.63 (*d*, $J=18$ Hz, C_8-H), 2.00 (*d*, $J=18$ Hz, C_8-H), 2.36 (*s*, 2.36 (*s*, 2H, C_6-H_2), 5.55 (*s*, 1H, C_4-H), 7.09-7.56 (*m*, 13H, Ar-*H*), 7.76-7.95 (*m*, 2H, Ar-*H*), 10.65 (*s*, 1H, NOH).

Fractions 5-10 were found by TLC to be a mixture of the above, ketone **16** and alcohol **12**. The last compound was obtained from fraction-12 by evaporation and trituration with ethanol ether; yield 10 mg; m.p. 216-18° (Found: C, 70.8; H, 7.1; N, 10.0. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%); M^+ at *m/z* 270; PMR (DMSO-d_6): δ 1.03 (*s*, 6H, $2\times CH_3$), 2.16 (*s*, 2H, C_6-H_2), 2.55 (*s*, 2H, C_8-H_2), 6.91 (*s*, 1H, C_4-H), 7.11-7.51 (*m*, 3H, Ar-*H*), 7.53-7.77 (*m*, 2H, Ar-*H*), 10.09 (broad *s*, 1H, OH), 11.11 (broad *s*, 1H, NH).

Fraction 13 gave a gummy solid becoming crystalline with ethanol, m.p. 224°. It was probably the betaine of **10a**; $M^{+\cdot}$ at *m/z* 343; PMR (DMSO-d_6): δ 1.00 (*s*, 6H, $2\times CH_3$), 2.72 (*s*, 2H, C_6-H_2), 2.95 (*s*, 2H, C_8-H_2), 7.27-7.63 (*m*, 3H, Ar-*H*), 7.95-8.30 (*m*, 2H, Ar-*H*), 7.82 (*s*, 5H, $N-C_6H_5$), 9.22 (*s*, 1H, C_4-H).

7,8-Dihydro-7,7-dimethyl-3-phenyl-5-6(H)-cinnolinone (**16**)

(a) Tetrahydroketone **2a** (0.5 g) was heated in pyridine (5 ml) on a water-bath for 16 hr and the solution diluted with water. The precipitate was filtered and recrystallised from methanol to give the starting material (0.4 g). The mother liquor was evaporated and the residue dissolved in ether. The ether solution first deposited crystals of **2a**, and then a yellow solid. The latter was recrystallised from ethanol to give **16** (50 mg), m.p. 121-23° (Found: C, 76.5; H, 6.5; N, 11.3. $C_{16}H_{16}N_2O$ requires C, 76.1; H, 6.4; N, 11.1%); $M^{+\cdot}$ at *m/z* 252; IR (nujol): $\nu C=O$ at 1690 cm^{-1}; PMR ($CDCl_3$): δ 1.15 (*s*, 6H, $2\times CH_3$), 2.63 (*s*, 2H, C_6-H_2), 3.30 (*s*, 2H, C_8-H_2), 7.35-7.65 (*m*, 3H, Ar-*H*), 8.03-8.25 (*m*, 2H, Ar-*H*), 8.22 (*s*, 1H, C_4-H).

(b) The above ketone was obtained in 30% yield by heating **2a** (1.3 g) with methanesulphonyl chloride (0.6 g) in pyridine (10 ml) on a water-bath for 16 hr. A much better yield (75%) was obtained by conducting the reaction with *p*-toluenesulphonyl chloride. In both cases, the reaction mixture was worked-up by evaporation of pyridine, addition of water and extraction of the product with ether.

(c) Hydrolysis of the oxime **7a** with acid provided another route to **16**. Thus, oxime **7a** (1 g), 10% sulphuric acid (20 ml) and dioxane (10 ml) were heated under reflux for 16 hr. The solvent was removed and the aqueous solution made ammoniacal. The precipitate was filtered and crystallized from ethanol to give the starting material **7a** (0.4 g) m.p. 258-62°. The mother liquor was evaporated and the residue fractionally crystallized from ether to give the oxime **7a** as the less soluble part (0.2 g) and ketone **16** (0.1 g) m.p. 120-22° as the more soluble fraction.

3-Phenyl-5-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydrocinnoline (**18**)

Ketone **16** (3.2 g) in methanol (30 ml) was treated with sodium borohydride (1 g) in portions. After 1 hr, solvent was removed and the residue treated with water. The resultant solid (3 g, m.p. 174-77°) was filtered and crystallised from ethanol-ether to give **18**, m.p. 181-82° (Found: C, 75.4; H, 7.4; N, 11.0. $C_{16}H_{18}N_2O$ requires C, 75.6; H, 7.1; N, 11.0%); $M^{+\cdot}$ at *m/z* 254; IR (nujol): νOH at 3180 cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 1.0 (*s*, 3H, CH_3); 1.20-2.35 (*m*, 2H, C_6-H_2), 2.95 (*s*, 2H, C_8-H_2), 4.85 (*m*, 1H, C_5-H), 5.40 (*brs*, 1H, OH); 7.25-7.60 (*m*, 3H, Ar-*H*), 7.85-8.20 (*m*, 2H, Ar-*H*), 8.15 (*s*, 1H, C_4-H).

It was also obtained by heating ketone **2a** (0.8 g) in dioxane (10 ml) and 3*N* hydrochloric acid (25 ml) under reflux for 4 hr. The solution was cooled and made alkaline. The gummy precipitate was recrystallised from ether to afford **18** (0.5 g), m.p. 177-80° identical with the above sample.

PPA rearrangement of the oximes **7**

The oxime **7a** (5 g) was heated with polyphosphoric acid (50 g) at 150° for 5 hr. The mixture was treated with ice and made ammoniacal. The product was filtered and recrystallized from ethanol to give the aminocinnoline **19a** (3.3 g), m.p. 209-11° (Found: C, 76.9; H, 6.2; N, 17.1. $C_{16}H_{15}N_3$ requires C, 77.1; H, 6.1; N, 16.9%); $M^{+\cdot}$ at *m/z* 249; IR (nujol): νNH_2 3230, 3330 cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 2.33 (*s*, 3H, CH_3), 2.47 (*s*, 3H, CH_3), 5.55 (*br s*, 2H, NH_2), 7.35-7.85 (*m*, 3H, Ar-*H*), 8.22-8.60 (*m*, 2H, Ar-*H*), 8.87 (*s*, 1H, C_4-H), 7.60 (*s*, 1H, C_8-H).

Compound **19a** was also obtained in 45% yield when a mixture of $POCl_3$ and pyridine was used instead of PPA and in quantitative yield by heating with 6 parts of conc. sulphuric acid at 120° for 10 min.

The oxime **7b** (18 g) was heated with PPA (180 g) to afford the aminocinnoline **19b** (16.5 g), m.p. 235-36° (Found: C, 70.4; H, 7.0; N, 22.6. $C_{11}H_{13}N_3$ requires C, 70.6; H, 7.0; N, 22.4%) [HCl salt: m.p. 268-71° (from methanol-ether)]; PMR (DMSO-d_6): δ 2.22 (*s*, 3H, CH_3), 2.43 (*s*, 3H, CH_3), 2.83 (*s*, 3H, C_3-CH_3), 4.60 (*br s*, NH_2), 7.50 (*s*, 1H, C_8-H), 8.13 (*s*, 1H, C_4-H).

The oxime **7c** (6 g) when treated with PPA (75 g) gave the aminocinnoline **19c** (2.7 g), m.p. 219-21° (from ethanol) (Found: C, 75.6; H, 5.3; N, 18.6. $C_{14}H_{11}N_3$ requires C, 76.0; H, 5.0; N, 19.0%); PMR (DMSO): δ 7.00 (*q*, 1H, C_6-H), 7.35-7.90 (*m*, 3H, Ar-*H*), 8.50-8.70 (*m*, 2H, Ar-*H*), 8.95 (*s*, 1H, C_4-H).

The oxime **14** likewise gave **19d** in 65% yield (from ethanol-ether), m.p. 206-7° (Found: C, 71.9; H, 7.8; N, 21.0. $C_{12}H_{15}N_3$ requires C, 71.6; H, 7.5; N, 20.9%); PMR ($CDCl_3$ + DMSO-d_6): δ 2.13 (*s*, 3H, C_6-CH_3), 2.39 (*s*, 3H, C_7-CH_3), 2.72 (*s*, 6H, C_3- and C_4-CH_3).

Compound **15** (1.4 g) was heated with PPA (20 g) for 7 hr at 130-140°. The mixture was cooled and treated with ice and excess ammonia. The green coloured product (**20**) was filtered off, yield 1.2 g, m.p. >300°. A sample was crystallized from aq. DMSO, m.p. >300° (Found: C, 64.4; H, 6.7; N, 17.4. $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.2; N, 17.1%); $M^{+\cdot}$ at *m/z* 227; IR (nujol): νNH_2 and νOH at 3440 and 3300 cm^{-1} respectively; νCO 1670 cm^{-1}; UV (MeOH): λ_{max} at 284 (sh), 294, 320 and 410 nm; UV (1 *N* HCl): 274 (sh), 286, 312 (sh), 324 (sh), 336 (sh) and 454 nm; PMR (DMSO-d_6): 2.08, 2.10, 2.26 (3*s*, each 3H, $3\times CH_3$), 5.45 (*s*, 2H, CH_2), 6.4 (*s*, 1H, =CH), 10.0 [*br s*, NH_2 (7)], 11.55-11.82 [*br s*, CO_2H (7)].

Chloroacetyl and pyrrolidinoacetyl derivatives of the amine **19b**

The amine **19b** (2.8 g) was dissolved in chloroform (150 ml) and THF (50 ml). The solution was mixed with sodium bicarbonate (2.5 g) in water (25 ml) and treated under stirring with chloroacetyl chloride (1.7 g) in chloroform (5 ml). After 4 hr, the chloroform layer was separated, washed with water, dried and evaporated. The residue was triturated with hexane and crystallized from chloroform-ether to give the chloroacetyl derivative **25a** (2.6 g), m.p. 265° (d) (Found: C, 58.8; H, 5.6; N, 15.8. $C_{13}H_{14}ClN_3O$ requires C, 59.2; H, 5.4; N, 15.9%).

The above chloroacetyl derivatives (2.5 g) was mixed with pyrrolidine (5 ml) when an exothermic reaction occurred. After further heating on a water-bath for 4 hr, the reaction mixture was treated with water and the product extracted with chloroform. Evaporation of the chloroform layer gave **25b** (2.2 g), m.p. 186-88°. (from ethanol-ether) (Found: C, 68.6; H, 7.5; N, 18.5. $C_{17}H_{22}N_4O$ requires C, 68.4; H, 7.4; N, 18.8%).

5-(N-Dichloroacetyl amino-6,7-dimethyl-3-phenyl-cinnoline (**26**)

The amine **19a** (4.2 g) was treated with dichloroacetyl chloride (2.5 g) as described above to give the dichloroacetyl derivative (**26**; 1.5 g), m.p. 224-26° (from acetone-ether) (Found: C, 60.4; H, 4.3; N, 11.9. $C_{18}H_{15}Cl_2N_3O$ requires C, 60.0; H, 4.2; N, 11.7%).

Deamination of 5-amino-3-phenyl-cinnoline (**19c**)

The aminocinnoline **19c** (1.1 g) was dissolved in conc. hydrochloric acid (3 ml) and water (10 ml) and the solution diazotised at 0° by treating with sodium nitrite (0.4 g) in water (3 ml). Hypophosphorous acid (10 ml) was then added at 0° and the mixture stirred for 1 hr at this temperature and at 28° for 16 hr. It was then filtered and the filtrate made ammoniacal. The greenish precipitate was filtered off and recrystallized from methanol to give 3-phenylcinnoline (0.1 g), m.p. 121-23°, undepressed by admixture with a sample obtained by decarboxylation of 3-phenyl-cinnoline-4-carboxylic acid[7] (Found: C, 81.3; H, 5.0; N, 13.6. $C_{14}H_{10}N_2$ requires C, 81.5; H, 4.9; N, 13.6%); PMR ($CDCl_3$): δ 7.20-8.67 (*m*, 9H, Ar-*H*), 8.05 (*s*, 1H, C_4-H).

Diazotisation of 5-amino-3,6,7-trimethyl-cinnoline (**19b**)

The aminocinnoline **19b** (1.1 g) was dissolved in boiling methanol (40 ml) containing benzene (10 ml). To the hot solution was added conc. sulphuric acid (1.2 g) followed by solid sodium nitrite (0.7 g) in small protions. The mixture was then heated under reflux for 4hr and cooled. The precipitated salts were filtered off. The filtrate was concentrated and diluted with water. The clear solution was made ammoniacal when the pyrazolocinnoline **22** separated out. It was filtered and recrystallised from DMF: yield; 0.8 g, m.p. >300° (Found: C, 66.7; H, 5.2; N, 28.4. $C_{11}H_{10}N_4$ requires C, 66.7; H, 5.1; N, 28.3%); $M^{+\cdot}$ at *m/z* 198; PMR (CF_3CO_2H): δ 3.0 (*s*, 3H, C_4-CH_3), 3.27 (*s*, 3H, C_8-CH_3), 7.97 (*s*, 1H, C_5-H), 9.58 (*s*, 1H, C_3- and C_9-H).

Schmidt reaction on ketone **16**

To a solution of the ketone **16** (1.2 g) in conc. sulphuric acid (5 ml) was added sodium azide (1 g) in small portions with cooling. After 2 hr, ice and excess ammonia were added. The precipitate was filtered and crystallized from ethanol to afford the aminocinnoline **19a** (0.9 g), m.p. and m.m.p. with an authentic sample, 206-8°.

Acid-catalyzed reactions of the oxime **7a**

(a) With phosphorous pentachloride

The oxime **7a** (1.3 g) was dissolved in THF (30 ml)

and chloroform (50 ml) and left with phosphorous pentachloride (2.1 g) at 0° for 4 hr and then at 28° for 16 hr. The solvents were removed *in vacuo* and the residue was treated with ice and ammonia and extracted with ether. The ether layer was evaporated to give a residue (1.5 g) from which again by extraction with ether and concentration, the pyridazino-azepinone **30** (0.15 g) was obtained. It was crystallised from ethanol; m.p. 230-31° (Found: C, 72.0; H, 6.7; N, 15.9. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%); $M^{+\cdot}$ at *m/z* 267; PMR ($CDCl_3$): δ 1.27 (*s*, 6H, 2 × CH_3), 2.30 (*s*, 2H, C_6-H_2), 3.13 (*s*, 2H, C_8-H_2), 7.25-7.55 (*m*, 3H, Ar-*H*), 7.67 (*s*, 1H, C_4-H); 7.85-8.25 (*m*, 2H, Ar-*H*), 10.0 (*s*, 1H, NH).

(*b*) *With formic acid*

The oxime **7a** (2 g) and 80% formic acid (40 ml) were heated under reflux for 6 hr. Removal of excess acid followed by addition of ice and ammonia gave a gummy product which became crystalline with ether. It was filtered and recrystallized from ethanol to give **2a** (0.5 g), m.p. and m.m.p. 239°; $M^{+\cdot}$ at *m/z* 254. The etheral filtrate was evaporated and the residue left in ethanol to give yellow crystals of the ketone **16** (0.1 g), m.p. and m.m.p. with an authentic sample, 118-20°. The mother liquor was evaporated and the residue left in ether-hexane to give a crop which on re-crystallization from hexane afforded **32** (0.1 g), m.p. 98-100° (Found: C, 80.1; H, 7.5; N, 11.8. $C_{16}H_{18}N_2$ requires C, 80.6; H, 7.6; N, 11.8%); $M^{+\cdot}$ at *m/z* 238; PMR ($CDCl_3$): δ 1.0 (*s*, 6H, 2 × CH_3), 1.58 (*t*, J = 7 Hz, 2H, C_6-H_2), 2.82 (*t*, J = 7 Hz, 2H, C_5-H_2), 2.97 (*s*, 2H, C_8-H_2), 7.25-7.60 (*m*, 3H, Ar-*H*), 7.45 (*s*, 1H, C_4-H), 7.90-8.20 (*m*, 2H, Ar-*H*).

The mother liquor from the above crystallisation was evaporated and the residue chromatographed over silica gel (15 g) using benzene-chloroform (1:3) as eluant. Fractions of about 25 ml were collected. The first two fractions gave the ketone **16**. Fractions 3 and 4 gave a mixture of **16** and **32**. Fractions 7 and 8 on evaporation gave the formamide **33** (0.15 g) which was crystallised from benzene, m.p. 176-78° (Found: C, 73.0; H, 7.10. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8%); $M^{+\cdot}$ at *m/z* 281; PMR ($CDCl_3$): δ 0.93 (*s*, 3H, CH_3), 1.08 (*s*, 3H, CH_3), 1.20-2.15 (*m*, 2H, C_6-H_2), 2.17 (*br s*, 2H, C_8-H_2), 5.30 (*m*, 1H, C_5-H), 7.25-7.55 (*m*, 4H, NH and Ar-*H*), 7.62 (*s*, 1H, C_4-H), 7.65-8.00 (*m*, 2H, Ar-*H*), 8.33 (*s*, 1H, CHO).

(*c*) *With 6N hydrochloric acid*

The oxime **7a** (1 g), 6*N* hydrochloric acid (20 ml) and dioxane (10 ml) were heated together under reflux for 7 hr. Dioxane was removed *in vacuo* and ammonia added to the residual solution. Extraction with chloroform and evaporation of solvent gave a gum which became crystalline with ether, yield 0.6 g, m.p. 155-65°; recrystallisation from ethanol gave slightly impure **34** (0.25 g), m.p. 167-69°. The reaction was then carried out with 4 times the quantity of reactants, extra hydroxylamine hydrochloride (3 g) being added. The total crude product (4 g), m.p. 110-40° was chromatographed over silica (60 g). Fractions of about 50 ml were collected. Initial elution was done with chloroform.

Seven fractions were combined and evaporated to give **34** (0.5 g), m.p. 170-72° (from ethanol) (Found: C, 67.3; H, 5.5; N, 10.0; Cl, 12.4. $C_{16}H_{15}ClN_2O$ requires C, 67.0; H, 5.3; N, 9.8; Cl, 12.4%); $M^{+\cdot}$ at *m/z* 286, 288; IR (nujol): νCO at 1720 cm^{-1}; PMR ($CDCl_3$): δ 1.22, 1.25 (2*s*, 6H, 2 × CH_3), 3.25 (*d*, J = 18 Hz, 1H, C_8-H), 3.63 (*d*, J = 18 Hz, 1H, C_8-H), 4.40 (*s*, 1H, C_6-H), 7.40-7.70 (*m*, 3H, Ar-*H*), 8.00-8.30 (*m*, 2H, Ar-*H*), 8.27 (*s*, 1H, C_4-H). Elution with chloroform—1% methanol (3 × 50 ml) gave a material (2 g) from which **36a** (0.75 g), m.p. 223° (d), was obtained by crystallisation from ethanol (Found: C, 69.8; H, 5.7; N, 13.4. $C_{32}H_{31}N_5O_4$ requires C, 69.9; H, 5.7; N, 12.8%); IR (nujol): νCO at 1720 cm^{-1}; PMR ($CDCl_3$ + DMSO-d_6): δ 1.12, 1.20, 1.30, 1.37 (4*s*, 3H each, 4 × CH_3), 3.08 (*br s*, 1H, OH), 3.38 (slightly *br s*, 4H, 2 × CH_3), 5.22 (*s*, 1H, CH − O), 7.25-7.80 (*m*, 2H, Ar-*H*), 7.85-8.30 (*m*, 2H, Ar-*H*), 8.42 (*s*, 1H, $C_4'-H$), 9.33 (*s*, 1H, C−H), 12.87 (*s*, 1H, NOH). Elution with chloroform—2% methanol (3 × 50 ml) gave a material (0.4 g) which on crystallisation from chloroform-methanol gave **36b** (~0.1 g), m.p. 218-20° (Found: C, 68.0; 68.0; 68.2; H, 6.7, 6.7, 6.7; N, 15.8; 15.6. $C_{32}H_{32}N_6O_4$ requires C, 68.1; H, 5.7; N, 14.9%).

The same chloroketone (**34**) was obtained in 15% yield when oxime **7a** (1.5 g) was heated under reflux for 4 hr with acetic acid saturated with HCl gas. The chloroketone was obtained in the more soluble fraction by fractional crystallization from methanol.

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Studies in Vilsmeier-Haack Reaction: Part XIX—Synthesis of Isoxazolo[3,2-*b*]quinazolone from 2-Hydroxy-3-methyl-4-quinazolone†‡

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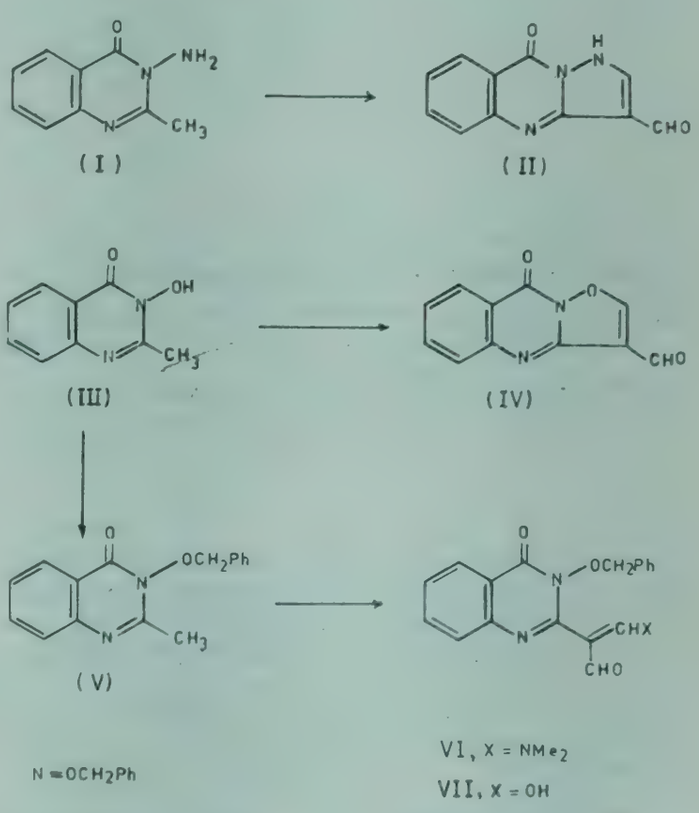
The Vilsmeier-Haack reaction on 3-benzyloxy-2-methyl-4-quinazolone (V) leads to the formation of dimethylaminoacrolein derivative (VI) which is converted into 3-benzyloxy-2-hetaryl-4-quinazolones and subsequently to 3-hydroxy-2-hetaryl-4-quinazolones. Attempted debenzylation followed by cyclisation to the isooxazolo [3,2-*b*] quinazolone system does not occur. The Vilsmeier reaction on the 3-benzoyloxy-2-methyl-4-quinazolone (XV) directly leads to 3-hydroxymethyl-2-isoxazolo-4-quinazolone (XVI) which on oxidation gives rise to the 3-formylisoxazolo [3,2-*b*] quinazolone (XVII).

Vilsmeier-Haack reaction on 3-amino-2-methyl-4-quinazolone (I) has earlier been reported[1] to result in an intensely fluorescent system, pyrazolo [5,1-*b*] quinazolone (II). Such mixed N, O heterocycles which are often intensely fluorescent[2], find uses in textile and other fields as fluorescent whitening agents. It was, therefore, of interest to synthesise the oxygen analogue (IV) of II by carrying out a similar reaction on 3-hydroxy-2-methyl-4-quinazolone (III).

The Vilsmeier reaction on III gave a dark brown product which was difficult to purify. However, this reaction on the benzyl derivative (V) resulted, as expected, in the formation of dimethylaminoacrolein derivative (VI). Hydrolysis of VI afforded the corresponding malondialdehyde (VII), thus supporting its structure. It was anticipated that debenzylation of either VI or VII could lead to the desired isoxazoloquinazolone (IV). However, attempts in this direction resulted in highly impure product which could not be purified. Reaction of VII with hydrobromic acid and pyridine gave in low yields a crystallisable material which analysed for the oxazinoquinazolone structure (VIII).

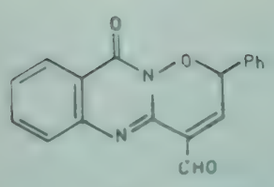
The dimethylaminoacrolein (VI) and malondialdehyde (VII) derivatives reacted readily with hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride to yield the corresponding heterocycles. These heterocycles could be debenzylated by hydrobromic acid to give the corresponding 3-hydroxy-2-hetaryl-4-quinazolones. The 3-hydroxy-2-isoxazolyl-4-quinazolone (XII) underwent ring cleavage in alkali to yield the cyanoacetaldehyde derivative (XIIIb) which however, failed to undergo cyclisation to give the cyanoisooxazoloquinazolone (XIV) under different conditions.



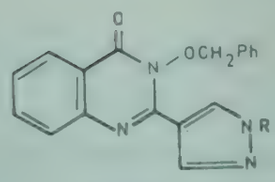
In view of the difficulties encountered in cyclising VII, we carried out the Vilsmeier reaction on the 3-benzoyloxy-2-methyl-4-quinazolone (XV). The product in the reaction was proved to have the 3-hydroxymethylisoxazoloquinazolone structure (XVI) based on the mass spectrum (*m/z* at 216 instead of 214 as expected for the 3-aldehyde). The IR spectrum also exhibited peaks at 3325 and at 1290 cm^{-1} corresponding to the −OH group. The structure was also confirmed by elemental analyses and by the Jones'

†A part of the Ph.D. thesis of S.B. Barnela, submitted to University of Bombay, 1976.

‡Part XVIII: *Indian J Chem*, **23B** (1984) 161.

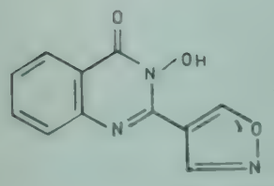


(VIII)

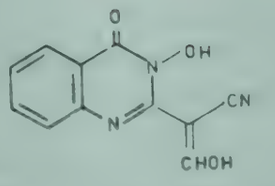


(IXa-b)

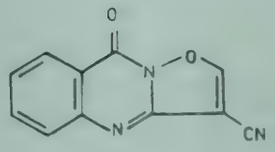
R ⟹ a: H; b: Ph



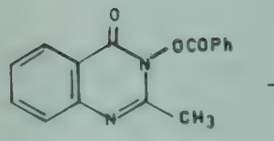
(XII)



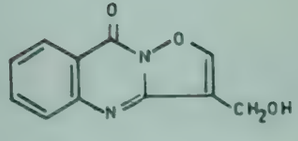
(XIII b)



(XIV)



(XV)



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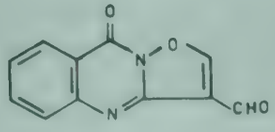
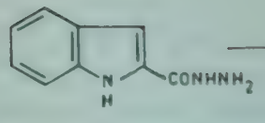
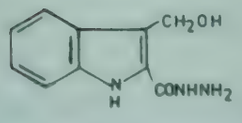


(XVII)



(XVIII)



(XIX)

oxidation of the XVI to the 3-formyl derivative (XVII). The aldehyde (XVII) gave a 2,4-DNP derivative. The PMR spectra of XVI and XVII could not be satisfactorily recorded due to poor solubility in various solvents. Both the compounds showed weak fluorescence in daylight.

The unusual formation of a reduction product, i.e. the alcohol (XIV) instead of the aldehyde (XX) in the Vilsmeier reaction has been reported[3] earlier during the formylation of indole-2-carboxyhydrazide (XVIII). But no mechanism has been suggested by these workers.

Experimental Procedure

All the melting points are uncorrected.

Vilsmeier reaction on 3-benzyloxy-2-methyl-4-quinazolone (V)

To the Vilsmeier reagent prepared from DMF (10 ml) and $POCl_3$ (0.022 mol), V (0.01 mol) in DMF (10 ml) was added. The reaction mixture was heated on a water-bath at 70-75° for 5 hr, poured into ice-water and basified with K_2CO_3 to *p*H 10. On warming on a water-bath for 15 min and cooling, the acrolein (VI) separated in 83% yield. It was crystallised from ethanol as pale yellow needles, m.p. 184-85° (Found: C, 68.8; H, 5.6; N, 11.6. $C_{20}H_{19}N_3O_3$ requires C, 69.2; H, 5.4; N, 12.0%).

2-(3-Benzyloxy-4-oxoquinazolinyl) malondialdehyde (VII)

The acrolein (VI, 1 g) was heated with NaOH (10 ml, 5%) at 80° for 30 min. The almost clear solution was filtered and acidified. The malondialdehyde (VII), which separated out in 90% yield, was crystallised from ethanol, m.p. 149-50° (Found: N, 8.5. $C_{18}H_{14}N_2O_4$ requires N, 8.7%).

4-Formyl-2-phenyl [1,2] oxazino [3,2-b]-quinazol-10-one (VIII)

A mixture of VII (1 g), pyridine (5 ml) and aq. HBr (7.5 ml, 40%) was left overnight at room temperature when VIII separated out as a pale yellow solid in 30% yield. It was crystallised from aq. ethanol as pale yellow needles, m.p. 115° (Found: C, 71.2; H, 4.3; N, 9.6. $C_{18}H_{12}N_2O_3$ requires C, 71.0; H, 4.0; N, 9.2%).

3-Benzyloxy-2-(4-pyrazolyl)-4-quinazolone (IXa)

A mixture of VII (0.0031 mol), hydrazine hydrate (80%, 0.0062 mol) and ethanol (10 ml) was refluxed for 2 hr. On cooling yellowish white needles separated out in 85% yield, which were recrystallised from aq. ethanol, m.p. 185-86° (Found: C, 67.5; H, 4.8; N, 17.8. $C_{18}H_{14}N_4O_2$ requires C, 67.9; H, 4.4; N, 17.6%).

3-Benzyloxy-2-(1-phenylpyrazol-4-yl)-4-quinazolone (IXb)

A mixture of VI (0.0028 mol) and phenylhydrazine (0.0033 mol) in ethanol (10 ml) was refluxed for 1 hr. The product separated on cooling in 76% yield was crystallised from ethanol as snowwhite needles, m.p. 171-72° (Found: C, 72.7; H, 5.0; N, 14.1. $C_{24}H_{18}N_4O_2$ requires C, 73; H, 4.6; N, 14.2%).

3-Benzyloxy-2-(4-isoxazolyl)-4-quinazolone (X)

A mixture of VI (0.0023 mol), NH_2OHHCl (0.0035 mol) and ethanol (10 ml) was refluxed for 2 hr. On cooling a yellow crystalline solid (X) separated out in 60% yield. It was crystallised from ethanol as long shining yellow needles, m.p. 149-50° (Found: C, 67.5; H, 4.3; N, 12.7. $C_{16}H_{13}N_3O_3$ requires C, 67.7; H, 4.1; N, 13.1%).

General procedure for debenzylation of 3-benzyloxy-2-hetaryl-4-quinazolones

After boiling the benzyloxy derivative (1 g) in aqueous HBr (10 ml, 40%) the solution was cooled and on adding the reaction mixture to water the product that separated out was filtered and treated with aq. sodium acetate. The products, their yields (%), m.ps, and crystallisation solvents respectively are given below. XIa, 85%, 281-82°; DMF; XIb, 85%, 203-04°, dioxan; XII, 63%, 264-65°; DMF; XIIIb, 55%; 270-71°, DMF.

2-[2-(3-Benzyloxy-4-oxo-quinazolinyl)] cyanoacetaldehyde (XIIIa)

The isooxazole (X, 1 g) was dissolved in NaOH solution (10 ml, 5%) by warming the mixture for 10 min and the resulting solution filtered. The filtrate on acidification with HCl gave XIIIa (80% yield), which crystallised from ethanol as white shining needles, m.p. 215° (Found: N, 13.0. $C_{18}H_{13}O_3$ requires N, 13.1%), IR: 2198 cm^{-1} ($\nu C \equiv N$).

3-Hydroxymethylisoxazolo [3,2-b] quinazol-9-one (XVI)

To the Vilsmeier reagent from DMF (12 ml) and $POCl_3$ (0.022 mol), a solution of XV (0.01 mol) in DMF (12 ml) was added. The reaction mixture was heated on a water-bath at 55-60° for 5 hr, cooled, poured into ice-water and basified with K_2CO_3 to *p*H 9. This was warmed at 60-65° for 30 min to a clear yellow solution, which was filtered, the filtrate cooled and acidified with HCl to *p*H 4. A yellow crystalline solid that separated out was filtered, and crystallised from dioxan to afford XVI as shining yellow needles, m.p. 284-85° (Found: N, 12.8. $C_{11}H_8N_2O_3$ requires N, 12.9%), IR: 3325 cm^{-1} (νOH), MS: *m/z* 216 (M^+).

Jones' oxidation of XVI

To a stirred solution of XVI (1 g) in dioxan (10 ml), Jones' reagent (8 ml) was added dropwise during 2 hr. On adding water to this green solution, XVII separated out as a whitish shining solid (70% yield), which crystallised from dioxan as white crystalline needles, m.p. 283-84°; IR: 1680 cm^{-1} (shoulder alongwith quinazolonecarbonyl).

2,4-DNP derivative of XVII was prepared as follows: A mixture of XVII (0.0046 mol), 2,4-DNP (0.0055 mol), 2 drops of conc. HCl and dioxan (15 ml) was heated for 10 min. On cooling, dark brown crystals that separated out (72% yield) were filtered and crystallised from dioxan, m.p. 290° (Found: C, 51.5; H, 3.0; N, 21.2. $C_{17}H_{10}N_6O_6$ requires C, 51.8; H, 2.5; N, 21.3%).

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Reaction of 2-Alkyl-4*H*-naphth[1,2-*d*][1,3]oxazin-4-ones with Primary Amines & Schiff Bases

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Condensation of 2-alkyl(methyl/ethyl)-4*H*-naphth[1,2-*d*][1,3]-oxazin-4-one (I) with primary amines results in 2,3-disubstituted benzo[*h*]quinazolin-4(3*H*)-ones (III, IV). While 3-alkyl-2-methylbenzo[*h*]quinazolin-4(3*H*)-ones with Schiff bases afford 3-aryl-2-styrylbenzo[*h*]quinazolin-4(3*H*)-ones (II) by replacement of ring nitrogen as well as styrylation of the methyl group, 2-methyl and 3-aralkyl-2-methyl compounds give 2-styryl derivatives (V) only.

A facile one-step synthesis of 3-aryl-2-styrylbenzo[*h*]quinazolin-4(3*H*)-ones (II) from 2-methyl-4*H*-naphth[1,2-*d*][1,3]oxazin-4-one (Ia) and schiff bases has been reported earlier[1] from our laboratories. Attempts have now been made to synthesise the corresponding 3-alkylquinazolinone derivatives.

When Ia was treated with schiff base, generated *in situ* from isopropylamine and benzaldehyde, in acetic acid at varying temperatures (30° to 100°C), no reaction took place. With a view to carrying out the reaction stepwise, styrylation of Ia with benzaldehyde under different conditions was tried again unsuccessfully. As an alternative, replacement of ring oxygen in Ia by alkylamino moiety and subsequent styrylation of the active methyl group was attempted. Thus, the reaction of Ia with isopropylamine in hot acetic acid yielded a colourless crystalline compound characterised as 3-isopropyl-2-methylbenzo[*h*]quinazolin-4(3*H*)-one (IIIc) based on spectral and microanalytical data. The reaction was extended to ammonia, methyl, benzyl, 4-methoxybenzyl, *n*-hexyl and cyclohexylamines and the corresponding IIIa, b, d-g (Chart 1, Table 1) were obtained in good yields.

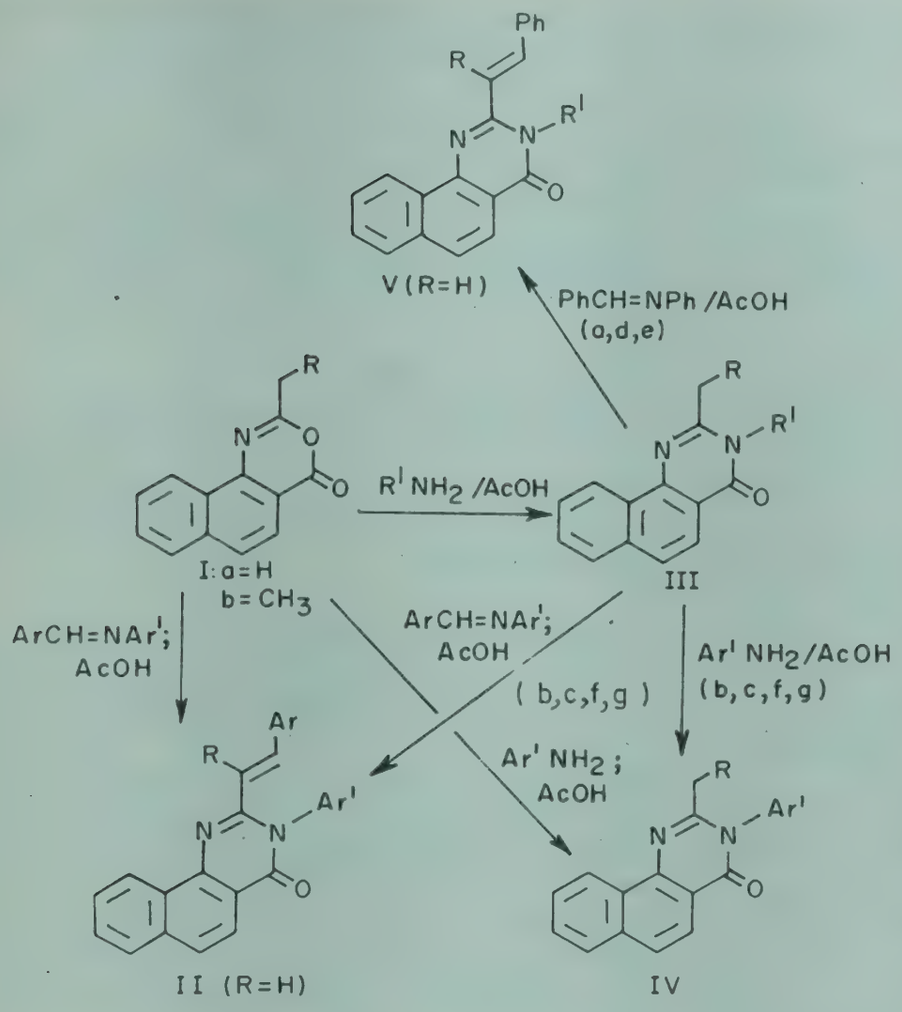
Compound (IIIc), however, did not undergo styrylation with benzaldehyde under different conditions studied. The reported ability of schiff bases to function as effective styrylating agents of active methyl group[1,2] prompted us to use them for this purpose. When IIIc was treated with benzylideneaniline in acetic acid, the result beyond our expectations, was the formation of 3-phenyl-2-styrylbenzo[*h*]quinazolin-4(3*H*)-one (IIa), characterised by direct comparison with an authentic sample[1]. Thus, benzylideneaniline not only effected styrylation of methyl group, but caused the replacement of the isopropylamino moiety by anilino function as well. Similar reaction of IIIc with different schiff bases resulted in the formation of corresponding II (Table 2). The ready replacement of the alkylamino moiety by arylamino component in these reactions may be attributed to the enhanced conjugation in the resulting product (II).

Ready formation of 2-methyl-3-phenylbenzo[*h*]quinazolin-4(3*H*)-one (IVa) from IIIc and aniline suggests the schiff base reaction to be a two-step process. Thus, styrylation of active methyl group precedes replacement of alkylamino group by

Table 1—Characterisation Data of 2,3-Dialkylbenzo[*h*]quinazolin-4(3*H*)-ones (III)

Compd	R′	m.p. °C	Yield %	Mol. formula	M⁺
		R = H			
IIIa	H	252	45	$C_{13}H_{10}N_2O$	210
IIIb	CH_3	178	58	$C_{14}H_{12}N_2O$	224
IIIc	Me_2CH	206	60	$C_{16}H_{16}N_2O$	252
IIId	$C_6H_5CH_2$	140	38	$C_{20}H_{16}N_2O$	300
IIIe	4-$MeOC_6H_4CH_2$	190	37	$C_{21}H_{18}N_2O_2$	—
IIIf	$H_3C(CH_2)_5$	186	43	$C_{19}H_{22}N_2O$	294
IIIg	Cyclohexyl	192	42	$C_{19}H_{20}N_2O$	292
		R = CH_3			
IIIh	H	268	43	$C_{14}H_{12}N_2O$	224
IIIi	CH_3	135	60	$C_{15}H_{14}N_2O$	238
IIIj	Me_2CH	232	57	$C_{17}H_{18}N_2O$	266
IIIk	$C_6H_5CH_2$	136	71	$C_{21}H_{18}N_2O$	—
IIIl	4-$MeOC_6H_4CH_2$	106	68	$C_{22}H_{20}N_2O_2$	—

IR(KBr): All the compounds showed $\nu C=O$ around 1670 cm^{-1}.
†PMR($CDCl_3$): IIIb—δ 2.67 (*s*, 3H, $C-CH_3$), 3.63 (*s*, 3H, $N-CH_3$), 7.45-7.82 (*m*, 6H, aromatic).
IIIc: δ 1.30 (*d*, 6H, $CH(CH_3)_2$), 1.84 (*s*, 3H, CH_3), 2.17 (*m*, 1H, CH), 7.30-7.76 (*m*, 6H, aromatic).
IIId: δ 2.41 (*s*, 3H, CH_3), 2.65 (*s*, 2H, CH_2), 7.25-8.28 (*m*, 11H, aromatic).
All the compounds gave satisfactory C, H and N analyses.



R = H	III R'	R = CH_3
a	H	h
b	methyl	i
c	isopropyl	j
d	benzyl	k
e	4-methoxybenzyl	l
f	n-hexyl	
g	Cyclohexyl	

R = H	IV Ar'	R = CH_3
a	phenyl	g
b	4-methyl phenyl	h
c	4-methoxy phenyl	i
d	4-chloro phenyl	j
e	2-nitrophenyl	k
f	3-nitrophenyl	l

Chart 1

Table 2—Characterisation Data of 3-Aryl-2-styryl (II), and 3-Aralkyl-2-styrylbenzo[*h*]quinazolin-4(3*H*)-ones (V)

Compd	Ar	Ar'	m.p. °C	Yield %	Mol. formula (M^+)
IIa	C_6H_5	C_6H_5	230[1]	80	$C_{26}H_{18}N_2O$
IIb	4-MeC_6H_4	C_6H_5	218[1]	74	$C_{27}H_{20}N_2O$
IIc	C_6H_5	3-$O_2NC_6H_4$	262	62	$C_{26}H_{17}N_3O_3$
IId	4-HOC_6H_4	C_6H_5	297	70	$C_{26}H_{18}N_2O_2$
IIe	2-HOC_6H_4	C_6H_5	286	68	$C_{26}H_{18}N_2O_2$ (390)
IIf	2-HOC_6H_4	4-MeC_6H_4	245	71	$C_{27}H_{20}N_2O_2$
IIg	4-$MeOC_6H_4$	4-MeC_6H_4	195	73	$C_{28}H_{22}N_2O_2$
		R			
Va	C_6H_5	H	238	70	$C_{20}H_{14}N_2O$ (298)
Vb	C_6H_5	$C_6H_5CH_2$	187	69	$C_{27}H_{20}N_2O$ (388)
Vc	C_6H_5	4-$MeOC_6H_4CH_2$	135	71	$C_{28}H_{22}N_2O$ (418)

IR(KBr): All the compounds showed $\nu C=O$ around 1670 cm^{-1}.
PMR($CDCl_3$): Vc: δ 3.76 (*s*, 3H, OCH_3), 5.50 (*s*, 2H, CH_2), 6.53-6.62 (*d*, 1H, olefinic), 6.70-8.19 (*m*, 14H, aromatic), 8.29 (*d*, 1H, olefinic), 9.12-9.20 (*d*, 1H, aromatic).
All the compounds gave satisfactory C, H and N analyses.

Table 3—2-Alkyl-3-arylbenzo[*h*]quinazolin-4(3*H*)-ones (IV)[a]

Compd	Ar′	m.p. °C	Yield (%)	Mol. formula ($M^{+\cdot}$)
		R=H		
IVa	C_6H_5	192[1]	80	$C_{19}H_{14}N_2O$
IVb	4-MeC_6H_4	172	56	$C_{20}H_{16}N_2O$ (300)
IVc	4-$MeOC_6H_4$	178	54	$C_{20}H_{16}N_2O_2$ (316)
IVd	4-ClC_6H_4	189	78	$C_{19}H_{13}N_2OCl$
IVe	2-$O_2NC_6H_4$	118	66	$C_{19}H_{13}N_3O_3$
IVf	3-$O_2NC_6H_4$	176	56	$C_{19}H_{13}N_3O_3$
		$R=CH_3$		
IVg	C_6H_5	176	83	$C_{20}H_{16}N_2O$ (300)
IVh	4-MeC_6H_4	186	70	$C_{21}H_{18}N_2O$
IVi	4-$MeOC_6H_4$	168	67	$C_{21}H_{18}N_2O_2$
IVj	4-ClC_6H_4	178	71	$C_{20}H_{15}N_2OCl$
IVk	2-$O_2NC_6H_4$	172	50	$C_{20}H_{15}N_3O_3$
IVl	3-$O_2NC_6H_4$	156	52	$C_{20}H_{15}N_3O_3$

[a]IR(KBr): All the compounds showed $\nu C=O$ around 1665 cm^{-1}. PMR($CDCl_3$): IVb: δ 2.36-2.44 (*d*, 6H, $2CH_3$), 7.2-8.3 (*m*, 10H, aromatic).

[b]All the compounds gave satisfactory C, H and N analyses.

arylamino moiety. IIIc could be converted into IVb-f (Table 3) by reaction with appropriate aromatic amines. The formation of IVa from IIIc probably involves nucleophilic attack by anilino nitrogen on carbonyl carbon of the latter, resulting in an open chain intermediate. Subsequent loss of element of aliphatic amine from the tautomeric form of the intermediate yields IVa.

The 3-unsubstituted (IIIa) and 3-aralkyl (IIId, e)-2-methylbenzo[*h*]quinazolin-4(3*H*)-ones proved to be exceptional in their reaction with both aromatic amines and schiff bases. With the former, replacement of nitrogen function did not take place. In the reaction of benzylideneaniline with these compounds, styrylation alone took place yielding V. Thus, ring NH and NCH_2Ar are found to be resistent to replacement by NAr′, which may be attributed to relatively less electrophilic nature of carbonyl carbon in the former (IIIa) due to tautomerism in the N−H free compound and to steric factors in IIId, e.

2-Ethyl-4*H*-naphth[1,2-*d*][1,3]oxazin-4-one (Ib) has been prepared for the first time from 1-amino-2-naphthalenecarboxylic acid and propionic anhydride. Condensation of Ib with different primary amines resulted in the corresponding 2-ethyl-3-substituted-benzo[*h*]-quinazolin-4(3*H*)-ones (IIIh-l; Table 1 and IVg-l; Table 3) characterised by spectral and analytical data. While the alkylamino moiety in IIIi,j could readily be replaced by arylamino group on reaction with aromatic amines to give IVg,h, the 3-unsubstituted and 3-aralkyl derivatives IIIh,k,l have been found to be resistant as in the methyl series. Styrylation of active methylene of the ethyl group in IIIi,j with the concommitant replacement of alkylamino by arylamino, however, did not take place, with schiff bases, perhaps due to steric reasons.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 283 B spectrophotometer, PMR spectra on Joel FX 90Q instrument using TMS as internal standard and mass spectra on Micro Mass 7070 H instrument.

2-Ethyl-4H-naphth[1,2-*d*][1,3]*oxazin-4-one* (*Ib*)

A mixture of 1-aminonaphthalene-2-carboxylic acid (1.87 g, 1 mmol) and propionic anhydride (10 ml) was refluxed for 4 hr and the solvent removed by distillation. The residue on recrystallisation from pet. ether (60-80°) using a little decolourising carbon gave Ib as a colourless crystalline solid (1.9 g, 84%), m.p. 89°; MS: M^+ at *m/z* 225; IR(KBr): 1740 cm^{-1} ($\nu C=O$) PMR($CDCl_3$): δ 1.45 (*t*, 3H, CH_2CH_3), 2.80 (*q*, 2H, CH_2CH_3), 7.26-8.82 (*m*, 5H, aromatic), 8.92 (*d*, 1H, $C_{10}-H$) (Found: C, 74.5; H, 4.9; N, 6.2. $C_{14}H_{11}NO_2$ requires C, 74.7; H, 4.9; N, 6.2%).

Condensation of 2-alkyl-4H-naphth[1,2-*d*][1,3]*oxazin-4-one* (*Ia, b*): (*i*) *With ammonia and methylamine*

Ia, b was taken in excess over ammonia or methyl amine solution and heated under reflux for 3-4 hr. The compound that separated in each case was filtered, washed with a few drops of ethanol and characterised as the corresponding 2,3-disubstituted benzo[*h*]quinazolin-4(3*H*)-one (IIIa, b, h, i; Table 1).

(*ii*) *With other primary amines*

To a solution of Ia,b (1 mmol) in acetic acid (2 ml) was added the appropriate amine (1 mmol) and heated on a steam-bath for 30 min and left aside. The crystalline IIIc-g, j-l (Table 1) and IVa-l (Table 3) that separated out were filtered and washed with a few drops of ethanol.

Reaction of 3-alkyl-2-methylbenzo[*h*]*quinazolin-4(3H)-ones* (*III*) *with schiff bases*

Compound (III, 1 mmol) in minimum quantity of acetic acid was treated with the required schiff base (1 mmol) at varying temperatures (30° to 100°) for 30 min and left aside. The resulting crystalline 3-aryl-2-styrylbenzo[*h*]quinazolin-4(3*H*)-ones (II), this obtained are included in Table 2. IIIa,d,e with

benzylideneaniline however, yielded respectively 2-styryl-(Va)-3-benzyl-2-styryl-(Vb)-and 3-(4-methoxybenzyl)-2-styryl-(Vc)-benzo[*h*]-quinazolin-4(3*H*)-ones.

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Synthesis of Substituted 2-(1′,3′,4′-Oxadiazol-2′-yl)indoles

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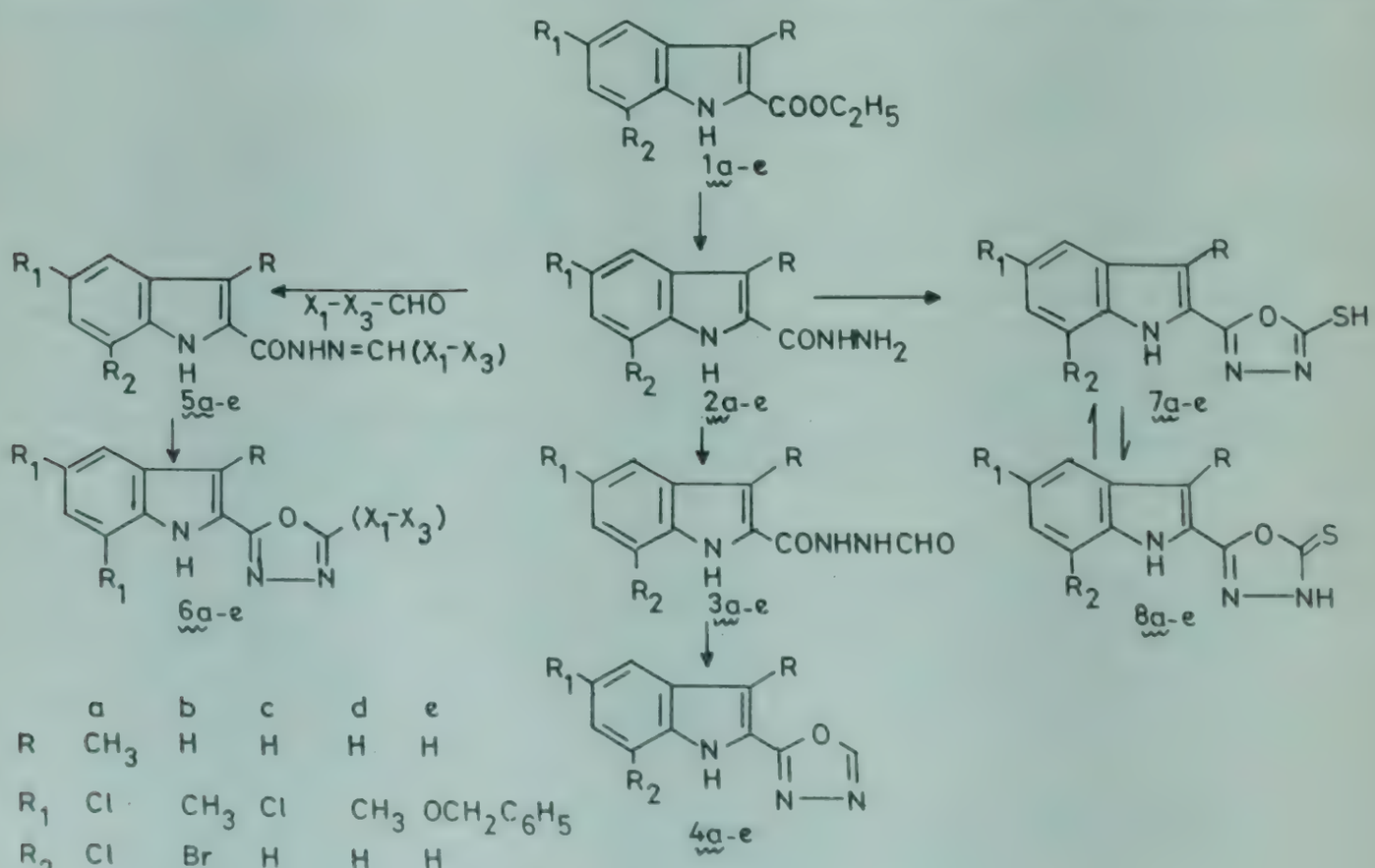
Substituted indole-2-carboxylic acid hydrazides (**2**) on refluxing with ethyl orthoformate give the respective 2-(1′, 3′, 4′-oxadiazol-2′-yl) indoles (**4**). These compounds have also been obtained by reacting **2** with formamide to get the corresponding N-formyl derivatives (**3**) which on cyclodehydration with $POCl_3$ furnish the above biheterocycles (**4**). 2-(5′-Substituted-1′, 3′, 4′-oxadiazol-2′-yl) indoles (**6**) have been prepared from the reaction of **2** with carboxaldehydes to yield the schiff bases (**5**) which on oxidative cyclisation with $FeCl_3$ afford the desired compounds. The hydrazides **2** when allowed to react with CS_2 in the presence of KOH give 2-(5′-thiono-1′, 3′, 4′-oxadiazolin-2′-yl) indoles (**8**).

The biological activity of 1, 3, 4-oxadiazoles[1-10] prompted us to synthesise the indolyloxadiazoles having substitutions in the indole and oxadiazole parts of the molecule.

The intermediate indolecarboxylic acid hydrazides (**2a-e**) were obtained by reacting substituted ethyl indol-2-carboxylates (**1a-e**) with hydrazine hydrate (80%) in ethanol under reflux. These were converted



	a	b	c	d	e
R	CH_3	H	H	H	H
R_1	Cl	CH_3	Cl	CH_3	$OCH_2C_6H_5$
R_2	Cl	Br	H	H	H

$X_1 = C_2H_5$, $X_2 = C_6H_5$, $X_3 = C_6H_4(OCH_3)$-p

Scheme 1

†IR ν_{max} in cm^{-1} and PMR chemical shifts in δ, ppm throughout the paper.

into the oxadiazolylindoles (**4a-e**) by two different routes[11] (Scheme 1). The acid hydrazides **2** on reaction with ethyl orthoformate under reflux gave 2-(1′, 3′, 4′-oxadiazol-2′-yl) indoles (**4a-e**; Table 1). These could also be obtained by formylating the hydrazides (**2a-e**) with formamide followed by cyclization of the resultant N-formyl derivatives (**3**) with phosphorus oxychloride. The IR† spectrum of **4a**, obtained by both the methods, displayed diagnostic bands at 1060, 1620 and 3300 due to C−O−C, C=N and NH functions respectively. Compound **3a** exhibited well resolved IR peaks at 3100, 3200, 1640 and 1660 for NH/NH, NH, C=O and CHO groups, respectively.

5′-Substituted oxadiazoles [**6a-e**$_{(x1-x3)}$; Table 1] were obtained by the oxidative cyclization of the schiff bases [**5a-e**$_{(x1-x3)}$; Table 1] with ferric chloride in acetic acid. The schiff bases (**5**) in turn were prepared by the reaction of various aldehydes with **2a-e**. The IR spectrum of compound **6a**$_{x3}$ displayed peaks at 1020, 1640, and 3400 for C−O−C, C=N and NH functions respectively. The PMR† spectrum of **6a**$_{x3}$ exhibited two distinct singlets at 2.58 and 3.68 due to methyl and methoxy protons respectively. The indole NH proton gave a broad singlet at 10.80 and rest of the aromatic protons appeared as a multiplet at 7.05-7.65. The compounds **6a-e**$_{(x1-x3)}$ gave characteristic IR and PMR spectra.

The reaction of **2a-e** with CS_2 and potassium hydroxide[12] furnished the substituted 2-(5′-thiono-1′, 3′, 4′-oxadiazolin-2′-yl) indoles (**8a-e**; Table 1) (Scheme 1). The IR spectrum of **8c** manifested characteristic peaks at 1060, 1380, 1640 and 3340 for C−O−C, C=S, C=N and NH functions respectively. The PMR spectrum revealed that the aromatic protons

Table 1—Characterization Data of Various Compounds Prepared

Compd	Yield (%)	m.p. °C	Nature (Crystallized form)	Mol. formula	Found (%), (Calc.)		
					C	H	N
2a	78	278	Colourless rectangular crystals (Dioxan)	$C_{10}H_9ON_3Cl_2$	46.3 (46.5	3.6 3.5	16.0 16.3)
2b[13]	41	273 (d) (273)	Pale yellow needles (Ethanol)	—	—	—	—
2c[14]	72	270	Pale yellow needles (Ethanol)	—	—	—	—
2d[14]	39	248	Yellow needles (Ethanol)	—	—	—	—
2e[14]	93	213-14	Colourless needles (Pyridine)	—	—	—	—
3a	56	280	Pale yellow needles (aq. Ethanol)	$C_{11}H_9O_2N_3Cl_2$	46.2 (46.2	3.0 3.2	14.4 14.7)
3c	62	320-21	Yellow silky needles (aq. ethanol)	$C_{10}H_8O_2N_3Cl$	50.3 (50.5	3.2 3.4	17.4 17.7)
4a*	52	203-5 (d)	Yellow microglobules (Benzene)	$C_{11}H_7ON_3Cl_2$	49.3 (49.3	2.9 2.6	15.5 15.7)
4b	50	207	Grey microglobules (Benzene)	$C_{11}H_8ON_3Br$	47.8 (47.5	2.6 2.9	14.8 15.1)
4c*	50	293-94	Yellow globules (Benzene)	$C_{10}H_6ON_3Cl$	54.8 (54.7	2.5 2.7	19.0 19.1)
4d	47	320	Yellow microneedles (Benzene)	$C_{11}H_9ON_3$	66.5 (66.3	4.4 4.5	20.9 21.1)
4e	55	208-10	Yellow microneedles (Benzene)	$C_{17}H_{13}O_2N_3$	69.8 (70.1	4.1 4.5	14.6 14.4)
5a$_{x1}$	75	197	Buff rectangular crystals (Ethanol)	$C_{13}H_{13}ON_3Cl_3$	52.6 (52.4	4.5 4.4	14.3 14.1)
5b$_{x1}$	73	182	Pinkish needles (Ethanol)	$C_{13}H_{14}ON_3Br$	50.8 (50.6	4.8 4.5	13.8 13.6)
5c$_{x1}$	80	201-2	Brownish needles (aq. Ethanol)	$C_{12}H_{12}ON_3Cl$	57.9 (57.7	4.9 4.8	17.0 16.8)
5d$_{x1}$	82	198	Colourless plates (Ethanol)	$C_{13}H_{15}ON_3$	68.4 (68.1	6.7 6.6	18.5 18.3)
5e$_{x1}$	78	195-96	Shining buff plates (Dioxan)	$C_{19}H_{19}O_2N_3$	71.8 (71.0	6.0 5.9	13.3 13.1)
5a$_{x2}$	81	226-28	Colourless needles (Ethanol)	$C_{17}H_{13}ON_3Cl_2$	59.2 (59.0	3.9 3.8	12.2 12.1)

(Contd.)

Table 1—Characterization Data of Various Compounds Prepared—(*Contd.*)

Compd	Yield (%)	m.p. °C	Nature (Crystallized form)	Mol. formula	Found (%), (Calc.)		
					C	H	N
$5b_{x2}$	88	259-62	Yellow needles (aq. Dioxan)	$C_{17}H_{14}ON_3Br$	57.2 (57.3	4.0 3.9	11.5 11.8)
$5c_{x2}$	78	268	Buff microneedles (Ethanol)	$C_{16}H_{12}ON_3Cl$	64.8 (64.5	4.0 4.0	14.4 14.1)
$5d_{x2}$	72	226	Pale yellow squares (Ethanol)	$C_{17}H_{15}ON_3$	73.4 (73.6	5.5 5.4	15.3 15.2)
$5e_{x2}$	76	205-6	Colourless needles (aq. Dioxan)	$C_{23}H_{19}O_2N_3$	75.0 (74.8	5.0 5.1	11.5 11.4)
$5a_{x3}$	76	225	Pale yellow needles (Dioxan)	$C_{18}H_{15}O_2N_3Cl_2$	57.3 (57.4	4.1 4.0	11.3 11.4)
$5b_{x3}$	76	234-35	Colourless needles (aq. Dioxan)	$C_{13}H_8O_2N_3Br$	55.9 (56.0	4.3 4.1	10.9 10.9)
$5c_{x3}$	68	279-80	Colourless needles (aq. Dioxan)	$C_{17}H_{14}O_2N_3Cl$	62.4 (62.3	4.4 4.3	12.1 12.8)
$5d_{x3}$	78	235-36	Colourless micro globules (aq. Dioxan)	$C_{18}H_{17}O_2N_3$	70.5 (70.4	5.7 5.5	13.9 13.7)
$5e_{x3}$	80	234-35	Colourless silky needles (aq. Dioxan)	$C_{24}H_{21}O_3N_3$	72.5 (72.2	5.5 5.3	10.6 10.5)
$6a_{x1}$	51	260-62	Colourless needles (Dioxan)	$C_{13}H_{11}ON_3Cl_2$	52.6 (52.7	3.6 3.7	14.0 14.2)
$6b_{x1}$	48	245 (d)	Pale yellow silky needles (Dioxan)	$C_{13}H_{12}ON_3Br$	51.0 (51.0	4.2 3.9	13.5 13.7)
$6c_{x1}$	46	244-45 (d)	Pale yellow globules (Dioxan)	$C_{12}H_{10}ON_3Cl$	58.3 (58.2	4.3 4.0	16.7 17.0)
$6d_{x1}$	54	268-70 (d)	Brownish powder (Dioxan)	$C_{13}H_{13}ON_3$	68.9 (68.7	5.9 5.7	18.4 18.5)
$6e_{x1}$	56	217-18	Brown powder (Dioxan)	$C_{19}H_{17}O_2N_3$	71.6 (71.5	5.6 5.3	13.1 13.2)
$6a_{x2}$	52	291 (d)	Colourless silky needles (Dioxan)	$C_{17}H_{11}ON_3Cl_2$	59.5 (59.3	3.4 3.2	12.1 12.2)
$6b_{x2}$	45	265-66 (d)	Colourless silky needles (Dioxan)	$C_{17}H_{12}ON_3Br$	57.8 (57.6	3.5 3.4	11.7 11.9)
$6c_{x2}$	48	260-62	Pale yellow globules	$C_{16}H_{10}ON_3Cl$	65.1 (65.0	3.2 3.4	14.5 14.2)
$6d_{x2}$	56	193-94 (d)	Brown micro globules (Benzene)	$C_{17}H_{13}ON_3$	73.8 (74.2	4.4 4.7	15.3 15.3)
$6e_{x2}$	53	187-88 (d)	Colourless silky needles (Dioxan)	$C_{23}H_{17}O_2N_3$	75.3 (75.2	4.9 4.6	11.5 11.4)
$6a_{x3}$	48	251-52 (d)	Colourless silky needles (Dioxan)	$C_{18}H_{13}O_2N_3Cl_2$	58.1 (57.8	3.2 3.5	11.4 11.2)
$6b_{x3}$	54	183-84 (d)	Grey micro needles (aq. Dioxan)	$C_{18}H_{14}O_2N_3Br$	56.4 (56.3	3.9 3.6	11.3 10.9)
$6c_{x3}$	52	271-72	Pale yellow needles (aq. Dioxan)	$C_{17}H_{12}O_2N_3Cl$	62.4 (62.7	3.5 3.7	13.2 12.9)
$6d_{x3}$	45	235 (d)	Yellowish needles (aq. Dioxan)	$C_{18}H_{15}O_2N_3$	71.0 (70.8	5.2 4.9	13.6 13.8)
$6e_{x3}$	51	185-87	Brownish needles (aq. Dioxan)	$C_{24}H_{19}O_3N_3$	72.8 (72.5	4.8 4.8	10.7 10.6)
8a	62	238-40	Yellow microneedles (Dioxan-ethanol)	$C_{11}H_7ON_3Cl_2S$	44.2 (44.0	2.1 2.3	14.2 14.0)
8b	62	238-40 235 (d)	Yellow needles (Dioxan-ethanol)	$C_{11}H_8ON_3BrS$	42.8 (42.6	2.4 2.6	13.4 13.5)
8c	58	248-49 (d)	Brown needles (aq. Ethanol)	$C_{10}H_6ON_3ClS$	48.0 (47.7	2.5 2.4	16.7 16.7)
8d	60	276-77 (d)	Yellow globules (aq. Ethanol)	$C_{11}H_9ON_3S$	57.5 (57.2	4.1 3.9	18.5 18.2)
8e	72	237-38 (d)	Pale yellow globules (Dioxan-ethanol)	$C_{17}H_{13}O_2N_3S$	63.0 (63.2	4.1 4.0	13.2 13.0)

*Compounds were also prepared from N-formylindole-2-carboxylic acid hydrazides.

resonated at 7.2-7.61 and the downfield peak (7.9) could be assigned to the indole NH proton. Another lowfield peak (11.65) was attributed to the resonance of oxadiazole NH. In confirmity with these assignments, both the NH were exchangeable with D_2O.

Biological activity

Some of the compounds prepared were screened for their antibacterial activity against *Esch. coli* and *Staph. aureus*. Amongst the substituted 2-(5'-thiono-1', 3', 4'-oxadiazol-2'-yl) indoles (**8a-e**), compound **8e** showed highest inhibition against *E. coli*. The carboxylic acid hydrazides (**2a-e**) and the schiff bases (**5a-e**) showed moderate inhibition against both the organisms. The activity of other compounds was not very significant.

Experimental Procedure

All the melting points are uncorrected and were recorded in a paraffin-bath. IR spectra were recorded on a Perkin-Elmer 297 spectrometer in nujol mull, PMR spectra on a Varian A-60 instrument in $CDCl_3$ using TMS as internal standard.

Substituted 2-(1',3',4'-oxadiazol-2'-yl) indoles (**4a-e**)

Indole-2-carboxylic acid hydrazide (**2a-e**, 0.005 mol) and ethyl orthoformate (25 ml) were heated under reflux for 12 hr. Excess of ethyl orthoformate was removed under reduced pressure and the residue treated with excess of pet. ether (b.p. 40-60°) and crystallized from an appropriate solvent to give **4** (Table 1).

Substituted N-formylindole-2-carboxylic acid hydrazides (**3a** *and* **3c**)

A mixture of the hydrazide **2a** or **2c** (0.0053 mol) and formamide (0.45 g, 0.01 mol) was heated at 180° for 4 hr, and excess of formamide removed *in vacuo*. The residue was dissolved in chloroform, washed twice with sodium bicarbonate solution, then with hydrochloric acid (10%) and finally with water, dried (Na_2SO_4) and solvent removed under reduced pressure. The resulting crude amide was crystallised from a suitable solvent (Table 1).

Cyclization of amides (**3a** *and* **3c**)

A solution of the amide **3a** or **3c** (0.005 mol) in phosphorus oxychloride (5 ml) was heated under reflux for 3 hr. The excess solvent was removed under reduced pressure and the residue dissolved in aq. acetic acid (10%) and filtered. The filtrate was neutralised with ammonia and the solid obtained was collected by filtration and crystallised from an appropriate solvent (Table 1).

Substituted N-alkylidene (arylidene) indole-2-carboxylic acid hydrazides [**5a-e**$_{(x_1-x_3)}$]

Appropriate aldehyde (0.00125 mol) was added to a suspension of **2a-e** (0.00125 mol) in ethanol (10 ml), and the reaction mixture heated under reflux for 5 hr. The product separated after cooling was filtered, washed with ethanol, dried and recrystallised from an appropriate solvent (Table 1).

Substituted 2-(5'-alkyl/aryl-1',3',4'-oxadiazol-2'-yl) indoles [**6a-e**$_{(x_1-x_3)}$]

To a solution of the schiff base [**5a-e**$_{(x_1-x_3)}$] (0.0005 mol) in acetic acid (100 ml), $FeCl_3$ (1 g) in water (4 ml) was added. The reaction mixture was stirred for 1 hr, water (150 ml) added to it until appreciable amount of solid separated out. It was allowed to stand for 2 days and the solid filtered, washed with water, dried and crystallised from an appropriate solvent (Table 1).

Substituted 2-(5'-thiono-1',3',4'-oxadiazolin-2'-yl)indoles (**8a-e**)

To a suspension of **2** (0.005 mol) in ethanol (12 ml), KOH (0.5 g) in water (3 ml) and CS_2 were added. The reaction mixture was heated under reflux till the evolution of H_2S ceased. Thereafter, it was cooled, diluted with water (50 ml) and acidified with conc. HCl. The solid that separated was collected by filtration, washed with water and crystallized from an appropriate solvent (Table 1).

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Studies on Oxidation of Triterpenoids: Part V—Oxidation of Friedelin with Selenium Dioxide in *t*-Butanol

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Friedelin (**2**) on prolonged heating with selenium dioxide in *t*-butanol furnishes two oxidised products, friedel-1(10)-en-4β-ol-2,3-dione (**5**) and 3α-acetyl-4-norfriedel-1(10)-en-3β-ol-2-one (**4**). The structures of **4** and **5** are based on spectral data (IR, UV, PMR, mass and ^{13}C NMR).

In earlier papers from our laboratory it was reported that SeO_2 oxidation in *t*-BuOH of triterpenoids containing *gem*-dimethyl group at C-4 led to the formation of α,β-unsaturated ketone[1]/epoxy ketone[2], depending on the amount of hydrogen peroxide added in the reaction mixture. Similar reaction on friedelin[3] (**2**), a 3-ketotriterpenoid with only one methyl group at C-4, failed to give either the α,β-unsaturated ketone or the epoxy ketone. However, later Anjaneyulu *et al.*[4] reported the isolation of friedel-1(2)-en-3-one (**1**) in the reaction of **2**. As **1** was required for some transformation reactions and since conversion of **2** into **1** was reported poor by other methods[5] we decided to carry this conversion with SeO_2 in *t*-BuOH. We envisaged the formation of friedel-2,3-dione (**3**) as a second possible product besides **1**. But to our surprise, none of these compounds was isolated, instead two highly oxidised products were isolated, the structure elucidation of which forms the subject matter of this paper.

The compounds (A) and (B) were isolated as detailed elsewhere in the paper (see Experimental). Compound-A analysed for $C_{30}H_{46}O_3$, m.p. 246-47°. IR spectrum of (A) exhibited a sharp peak at 3440 cm^{-1} indicating the presence of a non-hydrogen bonding tertiary hydroxyl group. The peak at 1705 cm^{-1} was due to a carbonyl group and the one at 1690 cm^{-1} was due to an α,β-unsaturated carbonyl group as supported by peaks at 1592 and 865 cm^{-1} due to double bond. The presence of α,β-unsaturated ketone in a five-membered ring was further supported by the UV spectrum of (A) which displayed λ_{max} at 237 nm (ε, 12,000). The mass spectrum of (A) showed the molecular ion peak at *m/z* 454 (M^+, 21.9); the other fragments of prominence appeared at *m/z* 439 (M^+-CH_3, 0.6), 412 (M^+-$COCH_2$, 37.3), 411 (4.1), 330 (0.2), 301 (2), 302 (2), 288 (330-$COCH_2$, 5), 261 (6), 222 (10), 205 (26.9), 190 (16.5), 177 (10.3), 163 (19.1).

The PMR spectrum of (A) was indicative of the presence of seven tertiary methyls which appeared as sharp singlets (3H each) at δ 0.96, 1.01, 1.05, 1.10, 1.19, 1.27 and 1.32. The peak due to three acetyl protons appeared at 2.22 and that due to OH proton at δ 4.01 (exchangeable with D_2O); the sharp one proton peak at 5.92 was due to a vinyl proton having no neighbouring proton. The absence of a peak corresponding to a methyl group and the doublet that was present in the parent **2** indicated that this methyl group has been converted into the acetyl group that appeared downfield at δ 2.22. These observations showed that C-4 got converted into a carbonyl group. The absence of any other peak between δ 2 and 5 indicated that the carbonyl groups did not have any α-protons and the hydroxyl group also did not contain any geminal proton indicating its tertiary nature. From the study of UV, IR and NMR spectra, the structure for the compound-A was proposed as 3α-acetyl-4-norfriedel-1(10)-en-3β-ol-2-one (**4**).

Carbon-13 NMR of (A) exhibited singlets at δ 203.75 and 198.35 due to the carbonyl carbons. The singlet at δ 174.34 and the doublet at 120.71 were assigned to carbons involved in α,β-unsaturated double bond-with respect to carbonyl group. The carbon containing the hydroxyl group appeared at δ 77.20 as a singlet. A comparison of ^{13}C NMR data of friedelin and compound-A is shown in Table 1.

Dreiding model of compound-A shows that the ring-A when five-membered should have the acetyl group below the plane and the hydroxyl group above the plane so as to minimise the interaction with the axial methyl on C-5. The hydroxyl proton would form hydrogen bonding with the two carbonyl groups on

Table 1—Comparison of Carbon-13 NMR Data of Friedelin and Compounds (A) and (B)

Carbon	Friedelin[7]	Compound-A	Compound-B
1	22.3 *t*	120.70 *d*	122.87 *d*
2	42.2 *t*	198.35 *s*	195.40 *s*
3	213.0 *s*	77.20 *s*	186.37 *s*
4	58.2 *d*	203.76 *s*	82.43 *s*
5	41.5 *s*	39.94 *s*	41.61 *s*
6	41.3 *t*	48.21 *t*	47.94 *t*
7	18.3 *t*	17.99 *t*	17.32 *t*
8	53.1 *d*	51.71 *d*	48.41 *t*
9	37.5 *s*	33.55 *s*	33.81 *s*
10	59.5 *d*	174.34 *s*	183.96 *s*
11	35.6 *t*	35.80 *t*	33.29 *t*
12	30.5 *t*	30.28 *t*	30.92 *t*
13	39.7 *s*	39.77 *s*	39.19 *s*
14	38.5 *s*	39.16 *s*	39.19 *s*
15	32.5 *t*	32.41 *t*	32.73 *t*
16	36.0 *t*	35.56 *t*	35.86 *t*
17	30.0 *s*	30.10 *s*	30.05 *s*
18	42.8 *d*	42.86 *d*	42.75 *d*
19	35.4 *t*	35.36 *t*	35.35 *t*
20	28.2 *s*	28.21 *s*	28.18 *s*
21	39.3 *t*	39.16 *t*	39.19 *t*
22	32.1 *t*	32.76 *t*	32.13 *t*
23	6.9 *q*	33.93 *q*	25.96 *q*
24	14.7 *q*	27.97 *q*	27.62 *q*
25	18.0 *q*	23.39 *q*	15.30 *q*
26	18.7 *q*	18.63 *q*	18.66 *q*
27	20.3 *q*	20.44 *q*	20.59 *q*
28	32.1 *q*	32.06 *q*	32.56 *q*
29	31.8 *q*	31.80 *q*	31.91 *q*
30	35.0 *q*	34.92 *q*	34.95 *q*

either side but the IR spectrum suggests the absence of such bonding. This fact is explained by assuming that the carbonyl groups being electronegative, repel each other and the acetyl methyl would have steric interaction with C-6 axial hydrogen. To minimise these interactions the acetyl carbonyl is directed farthest away and the acetyl methyl away from C-6 axial hydrogen. Thus the hydroxyl group is free and above the plane and this establishes the structure of compound-A as 3α-acetyl-4-norfriedel-1(10)-en-3β-ol-2-one (**4**).

Compound-B analysed for $C_{30}H_{46}O_3$, m.p. 272-78°. Its IR spectrum exhibited a sharp peak at 3440 cm^{-1} indicating the presence of a non-hydrogen bonded OH. Two sharp peaks at 1735 and 1680 cm^{-1} showed the presence of a six-membered ring ketone and an α,β-unsaturated ketone respectively, and the peaks at 1600 and 840 cm^{-1} were indicative of olefinic double bond in conjugation with a carbonyl group. The UV absorption at 278 nm (ε 8,600) indicated the presence of a typical α,β-unsaturated ketone as a chromophore. The mass spectrum had peaks at *m/z* 454 (M^+, 14), 439 ($M^+ - CH_3$, 6), 426 ($M^+ - CO$, 15), 412 ($M^+ - COCH_2$, 31), 411 ($M^+ - CO - CH_3$, 29), 395 (1), 302 (2), 301 (2), 287 (5), 273 (6), 259 (8), 219 (10), 205 (30), 191 (28), 163 (35), 150 (30), 95 (62), 55 (65), 43 (100). The PMR spectrum of (B) was completely different from that of compound-A though the IR and mass spectra appeared almost similar. The PMR spectrum of (B) was indicative of the presence of eight tertiary methyl groups which appeared at δ 0.98, 1.01, 1.02, 1.09, 1.19, 1.27, 1.29, and 1.38. The sharp singlet at δ 6.33 (1H) indicated the presence of a vinyl proton without any neighbouring proton.

The ^{13}C NMR spectrum of (B) was indicative of the presence of a teritiary carbon containing an OH at δ 82.43 as a singlet; the trisubstituted olefinic carbons appeared at δ 122.87 as a doublet and 183.95 as a singlet; two ketonic carbons appeared at δ 186.38 and 195.40 as singlets (Table 1). The presence of eight tertiary methyls in (B) showed that the C-4 carbon bearing a secondary methyl in the parent **2** got converted into tertiary carbon. The hydroxyl group was probably at C-4 as it did not show any geminal proton in its PMR spectrum and ^{13}C NMR confirmed the tertiary nature of C-4. Moreover, the absence of any peak in the region δ 2.3 to 3 showed the absence of protons alpha to carbonyl group. All the above facts lead us to assign structure (**5**) to compound-B.

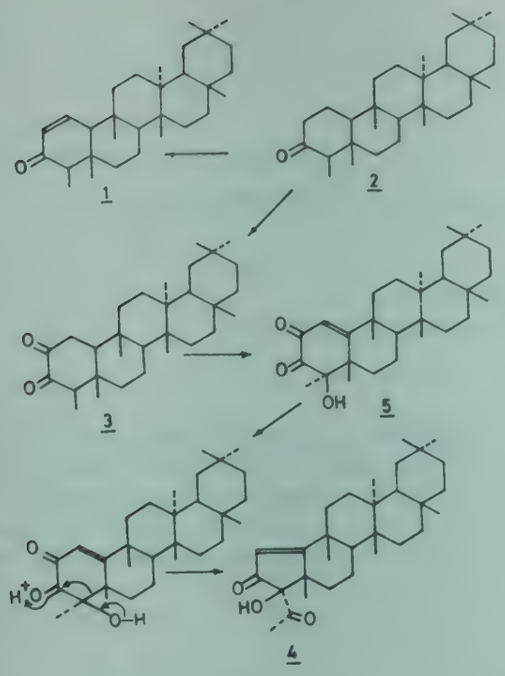
Dreiding model of (B) showed that in ring-A, C-1, 2, 4, 5 and C-10 are in the same plane and C-3 is below the plane. The methyl at C-4 being bulkier than the hydroxyl group, would prefer to remain equatorial and thus the hydroxyl group is situated axially above the plane, which makes the hydroxyl group appear as a non-hydrogen bonded sharp peak in the IR spectrum. These spectral evidences indicate that compound-B could be assigned the structure as friedel-1(10)-en-4β-ol-2,3-dione (**5**).

The formation of **4** and **5** from **2** can be rationalised as follows:

The active methylene at C-2 of friedelin (**2**) is first oxidised by SeO_2 to a 2,3-diketone (**3**) as suggested earlier[3], which would further undergo concerted dehydrogenation to furnish the olefinic double bond at $C_1 - C_{10}$ and hydroxylation[6] at C-4 by SeO_2 to give rise to **5**. The compound (**5**) being strained due to the presence of two carbonyl groups and an olefinic double bond, relieves its strain by undergoing rearrangement, as proposed in the Scheme 1, to furnish **4**.

Experimental Procedure

A mixture of friedelin (1.5 g), Selenium dioxide (1.5 g) and *t*-BuOH was refluxed for 24 hr under nitrogen atmosphere. The solvent was distilled off under reduced pressure and the residue extracted with ether, the organic layer washed with water and dried (Na_2SO_4). The residue obtained after removal of ether



Scheme 1

was chromatographed over silica gel column. Two products (A and B) isolated from the column were purified by crystallisation from $CHCl_3$-MeOH.

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Conformational Preferences About $N_{sp^2} - C_{sp^2}$ Bond in N-Aryl- & N-(2′-Pyridyl)-camphorimides: A PMR Study

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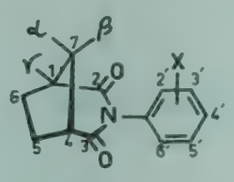
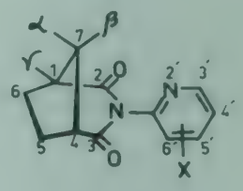
A number of N-aryl- and N-(2′-pyridyl)-camphorimides (I-XII) have been prepared and their conformational analysis about the $N_{sp^2} - C_{sp^2}$ bond has been studied by PMR spectroscopy. The shielding parameters of β-methyl and *o*-substituent resonances demonstrate restricted rotation and non-planar conformations about the N − C bond and the preference of the sterically favoured conformation. Steric and electronic requirements of the sp^2-hybridised nitrogen lone-pair are found to be effective in controlling the conformation about the N − C(pyridyl) bond. ^{13}C NMR studies do not provide any valuable information about the different conformations.

High energy barrier and non-planar conformation about the N − C(phenyl) bond in N-arylsuccinimides have been demonstrated earlier with the help of asymmetric cage moieties employing a number of Diels-Alder adducts of maleic anhydride with anthracene, cyclopentadiene, cycloheptatriene, cyclooctatetraene, β-naphthol and naphthalene[1-3]. Two sharp singlets for the tolyl methyl protons ($\Delta\delta$ 1.02) in the PMR spectrum of the compound **1**[2] exhibited the presence of two conformers in the ratio 1:1.18 which was evaluated with the help of the relative intensities of the signals; on the other hand the compound **2**[4] showed the presence of a preferred conformation about the N − C bond as only a singlet (δ 1.10) was observed for the picolyl methyl protons. Torsional barrier to rotation about the N − C bond in the system has been attributed to the steric interaction of the *ortho*-substituent with one of the imidyl carbonyls in the transition state. The moieties employed for the conformational analysis of N-arylsuccinimidyl system are effective probes but may have certain limitations also. In the *syn*†-conformation the π-electron cloud of the moiety has some significant interaction with the *ortho*-substituent and may control the conformational population. To overcome this π-electronic interaction with the *o*-substituents we have employed camphorimidyl moiety for conformational analysis. The two methyls (β and γ) of the camphorimidyl moiety have been shown to be an efficient probe for determining the restricted rotation and non-planar conformation about the N − N and N − CO bonds[5]. A number of N[aryl (I-IX) and N-pyridyl (X-XII) (Table 1) derivatives of camphorimide have been prepared and their conformational analysis about the N − C bond has been described in this paper.





I	X = H	X	X = H
II	X = o-CH_3	XI	X = 6′-CH_3
III	X = 2′,6′-dimethyl	XII	X = 4′,6′-dibromo
IV	X = 2′-CH_3, 6′-Cl		
V	X = 2′-CH_3, 4′,6′-dibromo		
VI	X = 2′-CH_3, 3′-Cl		
VII	X = o-OCH_3		
VIII	X = m-CH_3		
IX	X = m-OCH_3		

Ortho-Substituted N-Phenylcamphorimides

The PMR spectrum of N-phenylcamphorimide (I) exhibited three sharp signals for α-, β- and γ-methyls and normal resonances for the other protons (Table 2). The assignment of the three methyl signals of camphorimide was made with the help of $Eu(DPM)_3$ shift reagent[6]. Free rotation about N − C(phenyl) bond in N-phenyl succinimidyl system has been reported[2] and such a behaviour is expected in this compound also. The shift in the β-methyl resonances ($\Delta\delta$ 0.21) indicated an average paramagnetic effect of the N-phenyl due to free rotation about the N − C bond.

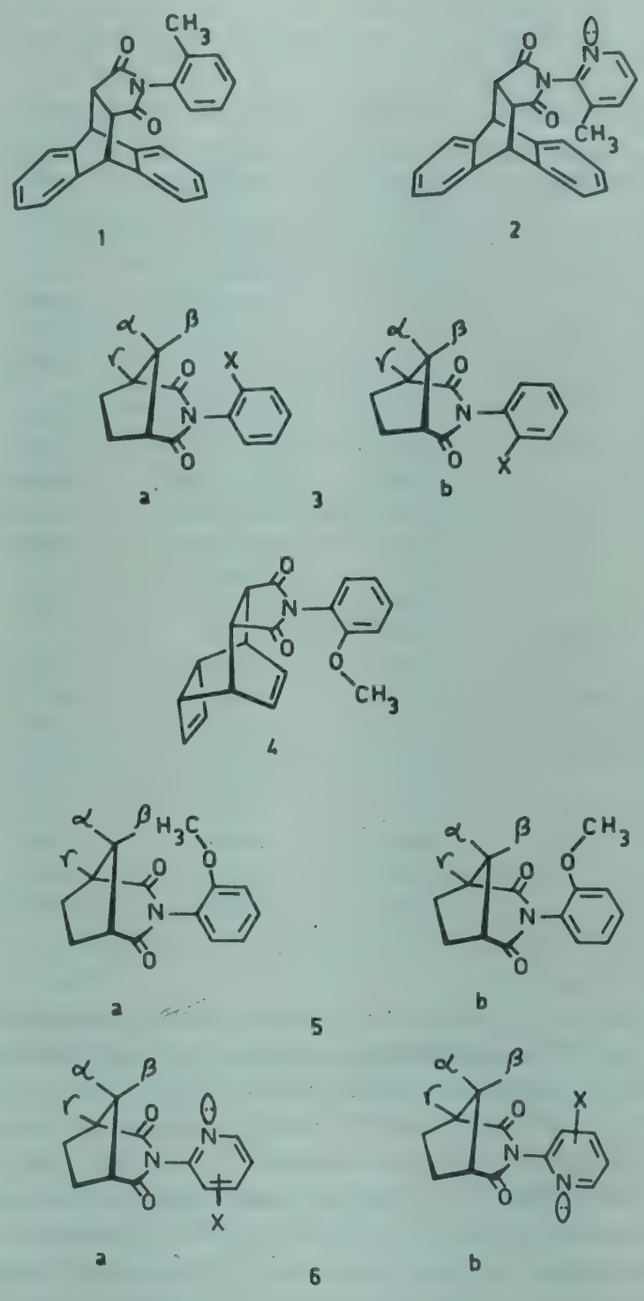
The spectrum of N-(*o*-tolyl)camphorimide (II) exhibited three sharp singlets at δ 1.07 (3H), 1.24 (2H) and 1.27 (4H) for the α-, β- and γ-methyls and two singlets at 2.10 (2H) and 2.20 (1H) for the tolyl methyl protons along with other resonances (Table 2). Multiplicity in the *o*-tolyl resonances and β-methyl

† *o*-Substituent of the phenyl ring lies towards the cage moiety.

Table 1 – Characterization Data of Compounds I-XII

Compd*	m.p. °C	Mol. formula	Found (%) (Calc)	
			C	H
I	120	$C_{16}H_{19}NO_2$	74.2	7.3
			(74.7	7.4)
II	107	$C_{17}H_{21}NO_2$	74.9	7.7
			(75.3	7.8)
III	138	$C_{18}H_{23}NO_2$	75.3	7.9
			(75.8	8.1)
IV	173	$C_{17}H_{20}NO_2Cl$	67.0	6.7
			(66.9	6.6)
V	157	$C_{17}H_{19}NO_2Br_2$	47.1	4.4
			(47.6	4.4)
VI	143	$C_{17}H_{20}NO_2Cl$	66.4	6.5
			(66.9	6.6)
VII	138	$C_{17}H_{21}NO_3$	70.8	7.1
			(71.1	7.4)
VIII	125	$C_{17}H_{21}NO_2$	75.0	7.7
			(75.3	7.8)
IX	128	$C_{17}H_{21}NO_3$	70.9	7.3
			(71.1	7.4)
X	101	$C_{15}H_{18}N_2O_2$	69.3	6.9
			(69.7	7.0)
XI	140	$C_{16}H_{20}N_2O_2$	70.4	7.2
			(70.6	7.4)
XII	195	$C_{15}H_{16}N_2O_2Br_2$	40.7	3.6
			(41.1	3.7)

*IR spectra exhibited bands characteristic of various functions present in the compounds.



resonances suggested a slow rate process about the N – C(phenyl) bond and the presence of two conformers. In one of the conformers with tolyl methyl *syn* to the β-methyl (**3a**; X = CH_3), an intramolecular Van der Waal repulsion[7,8] causes some mutual deshielding on both β and tolyl methyls and the deshielded value of *o*-tolyl methyl resonances would correspond to the *syn*-conformation (**3a**). The β-methyl signal which overlaps with the γ-methyl resonances indicated the conformation **3a** where it attains a similar magnetic environment as that of the γ-methyl. The β-methyl signal at δ 1.24 corresponds to the *anti*-conformation and the conformer population ratio 1:2 could be derived from their relative intensities which show the preference of the sterically favoured conformation **3b**. The proposed conformations (**3a, 3b**) were supported by the spectral data of compound III where only one conformation would be possible. Two singlets each of three protons for the 2′- and 6′-methyl protons ($\Delta\delta$ = 0.1) and a singlet for the β-methyl exhibited a non-planar conformation about the N – C bond.

In nitrobenzene the spectral pattern of compound II remained unchanged and the variable temperature spectral studies showed that the *o*-tolyl methyl signals coalesce at 95° and the energy barrier to rotation about the N – C(phenyl) bond was found to be 83.6 kJ/mol with the help of Eyring's rate equation[9,10]. In *syn*-conformation the tolyl methyl and β-methyl are fairly close together and would exhibit NOE phenomenon. Some decoupling experiments were carried out on a 300 MHz instrument but even then the signals ($\Delta\delta$ 0.03) remained so close together that it was quite difficult to manipulate for some convincing results.

The existence of two non-planar conformations about the N – C(phenyl) bond at the probe temperature is evident from the duplicity in the β-methyl and 2′-methyl resonances in the spectrum of compound IV (Table 2). The signal due to β-methyl protons which overlaps with γ-methyl resonances was assigned for the *syn*‡-conformation (**3a**) while the

‡ *syn* refers to 2′-methyl being *endo* to β-methyl in compounds IV and V.

Table 2 – Characteristic PMR Spectral Data of N-Aryl- and N-pyridyl-camphorimides (in δ, ppm)

Compound	α-CH_3	β-CH_3	γ-CH_3	5-H,6-H	4-H	X	Aromatic
Camphoric anhydride	1.02 (*s*,3H)	1.10 (*s*,3H)	1.27 (*s*,3H)	2.10 (*m*,4H)	2.87 (*m*,1H)	—	—
I	1.05 (*s*,3H)	1.22 (*s*,3H)	1.27 (*s*,3H)	2.13 (*m*,4H)	2.88 (*m*,1H)	—	7.25 (*m*,5H)
II	1.07 (*s*,3H)	1.24,1.27 (*ds*,2:1,3H)	1.27 (*s*,3H)	2.17 (*m*,4H)	2.92 (*m*,1H)	2.10,2.20 (*ds*,2:1,3H)	7.35 (*m*,4H)
III	1.06 (*s*,3H)	1.27 (*s*,3H)	1.24 (*s*,3H)	2.10 (*m*,4H)	2.89 (*m*,1H)	2.03,2.13 (*s*,3H)(*s*,3H)	7.00 (*m*,3H)
IV	1.00 (*s*,3H)	1.22,1.35 (*ds*,1:1.72,3H)	1.22 (*s*,3H)	2.15 (*m*,4H)	2.82 (*m*,1H)	2.05,2.15 (*ds*,1.72:1,3H)	7.15 (*m*,3H)
V	1.04 (*s*,3H)	1.24,1.43 (*ds*,2:1,3H)	1.24 (*s*,3H)	2.23 (*bm*,4H)	2.85 (*bm*,1H)	2.08,2.16 (*ds*,1:2,3H)	7.80 (*m*,2H)
VI	1.00 (*s*,3H)	1.17,1.23 (*ds*,2:1,3H)	1.23 (*s*,3H)	2.10 (*m*,4H)	2.84 (*m*,1H)	2.03,2.07 (*ds*,2:1,3H)	7.10 (*m*,3H)
VII	1.04 (*s*,3H)	1.22,1.29 (*ds*,2:1,3H)	1.26 (*s*,3H)	2.12 (*m*,4H)	2.83 (*m*,1H)	3.80 (*bs*,3H)	7.20 (*m*,4H)
VIII	1.02 (*s*,3H)	1.18 (*s*,3H)	1.23 (*s*,3H)	2.09 (*m*,4H)	2.83 (*m*,1H)	2.33 (*s*,3H)	7.00 (*m*,4H)
IX	1.03 (*s*,3H)	1.20 (*s*,3H)	1.25 (*s*,3H)	2.08 (*m*,4H)	2.83 (*m*,1H)	3.76 (*s*,3H)	6.90 (*m*,4H)
X	1.07 (*s*,3H)	1.28 (*s*,3H)	1.28 (*s*,3H)	2.15 (*m*,4H)	2.85 (*m*,1H)	—	7.50,8.90 (*dm*,4H)
XI	1.07 (*s*,3H)	1.37 (*s*,3H)	1.28 (*s*,3H)	2.18 (*m*,4H)	2.89 (*m*,1H)	2.15 (*s*,3H)	7.50,8.67 (*dm*,3H)
XII	1.05 (*s*,3H)	1.28 (*s*,3H)	1.28 (*s*,3H)	2.25 (*m*,4H)	2.82 (*m*,1H)	—	8.25,8.66 (*dm*,2H)

signal at δ 1.35 (1.9H) for the other conformation (**3b**). Chlorine has a higher deshielding effect on β-methyl and the conformation **3b** is favoured due to the smaller size of chlorine than the methyl group (1.72:1). In compound V with a bromine at 6′-position, similar multiplicities in the spectrum were observed (Table 2). However, in this case *syn*-conformer (**3a**) appears to be favourable due to smaller size of the methyl group (conformer ratio 2:1). A chlorine substituent at 3′-position as in compound VI also exhibited similar spectral behaviour and even the conformational population was similar to that of compound II (1:2). Fractional crystallization of all these compounds and a single spot in TLC indicated the absence of atropisomers.

The appearance of two singlets for β-methyl protons (δ 1.22, 2H; δ 1.29, 1H) and a singlet (δ 3.80, 3H) for the *o*-OCH_3 protons ($W_{1/2}$ = 3Hz) suggests the presence of two non-planar conformers (**3a** and **3b**) (Table 2). A preferred arrangement about the aryl C(2′)–O bond has been reported[3,11] for the *syn*-conformation of N-(*o*-anisyl)camphorimide (**4**). In *syn*-conformation, the conformer **5a** about the C(2′)–O bond would be forbidden and in the absence of desired multiplicity in *o*-OCH_3 resonances, hindered rotation about the N–C bond is only evident. The downfield β-methyl signal (δ 1.29) corresponded to *syn*-conformation (**3a**) due to the electronegativity of oxygen atom.

Free rotation about the N–C bond in N-(*m*-substituted phenyl)-succinimide has been inferred through the PMR spectral studies.[2] However, a small buttressing effect of the *meta*-substituents on *ortho*-hydrogens of biphenyls has been reported on the basis of their half-life periods for recemization[12]. The spectra of *meta*-derivatives (VIII and IX) did not show any multiplicity in their resonance signals as the buttressing effect of the *meta*-substituents was not sufficient for restricting the rotation about the N–C bond. The average value of β-methyl resonances and the absence of multiplicity in the signal for *m*-substituent showed a free rotation about the N–C bond. The spectrum of compound VIII at 0° did not show any multiplicity in the methyl resonances and suggested free rotation.

The ^{13}C NMR spectra of compounds II and VII did not show multiplicity in the *o*-substituent and β-methyl resonances (Table 3). Compound III exhibited a similar spectrum as that of II and demonstrated the equivalence of 2′- and 6′-methyls (Table 3). Evidently, ^{13}C NMR spectroscopy did not provide any valuable information which might be helpful in conformational analysis as the resonances were least affected by anisotropic interactions.

Table 3 – ^{13}C NMR Spectral Data of the Compounds I, II, III and VII (in δ, ppm)

I	13.97(C_α), 21.83(C_β), 25.29(C_γ), 56.61(C_1), 177.96(C_2), 175.79(C_3), 19.28(C_4), 34.23(C_5), 43.98(C_6), 54.55(C_7) & 134.89-128.06 (aromatic carbons).
II	13.92(C_α), 21.88(C_β), 25.46(C_γ), 56.88(C_1), 177.63(C_2), 175.57(C_3), 19.28(C_4), 34.40(C_5), 44.15(C_6), 54.55(C_7), 16.79(o-CH_3 carbon) and 136.46-126.60 (aromatic carbons).
III	13.97(C_α), 22.37(C_β), 25.84(C_γ), 56.93(C_1), 177.36(C_2), 175.52(C_3), 19.61(C_4), 34.61(C_5), 44.31(C_6), 54.93(C_7), 17.22(2′,6′-dimethyl carbons) and 136.30-128.61 (aromatic carbons).
VII	13.97(C_α), 22.21(C_β), 25.51(C_γ), 56.77(C_1), 177.58(C_2), 175.52(C_3), 19.44(C_4), 34.56(C_5), 44.31(C_6), 54.55(C_7), 55.69(o-OCH_3 carbon) and 155.37-111.87 (aromatic carbons).

sp^2-Hybridised Lone-Electron Pair Interactions on Conformational Rate Processes about the N – C(pyridyl) Bond

Sutherland[13] and Bockelheide[14] have shown that pyridyl nitrogen lone-pair has appreciably smaller steric interactions than an aromatic C – H bond. Nasipuri *et al.*[15] observed that the steric requirements of nitrogen lone-pair in quinoline is less than that of a hydrogen atom. Restricted rotation about the N – C(pyridyl) bond has been demonstrated with the help of N-2′-pyridyl imide derivatives of some Diels-Alder adducts[4]. The torsional barriers in these systems were attributed to the interaction of sp^2-hybridised lone-pair electrons of nitrogen and the imidyl carbonyls in the transition states. Invariably, the preferred non-planar conformation was observed in N-(2′-pyridyl)succinimides where sp^2-hybridised nitrogen lone-pair of the pyridyl moiety lies *anti* to the cage moiety and the steric requirements of the lone-pair is even greater than that of a methyl group in terms of repulsive forces[16] with the π-electrons in the system.

Slow rate process about the N – C bond is also expected in compound XI and the absence of splitting in β-methyl and picolyl methyl resonances suggested a preferred non-planar conformation about the N – C bond (Table 1). In one of the two conformations, the lone-pair of nitrogen would be *syn* to the β-methyl (**6a**) while in the other it would be *anti* (**6b**) to the β-methyl. Deshielding parameter of the β-methyl, group ($\Delta\delta$ .027) suggests the sp^2-hybridised lone-pair to be in *syn*-arrangement (**6a**). β-Methyl did not exhibit similar behaviour as that of compound II (**3a**) and provided evidence for the absence of the conformer **6b**.

N-(4′,6′-Dibromo-2′-pyridyl)camphorimide (XII) exhibited two sharp singlets for α-, β- and γ-methyl protons along with other resonances (Table 2). 6′-Bromine may provide some convincing evidence for the non-planar conformations particularly when it lies *syn* to the β-methyl. Spectral pattern of the compound suggested a preferred non-planar conformation about the N – C bond. The deshielding parameter of β-methyl indicated its interaction with the sp^2-hybridised nitrogen lone-pair similar to compound XI. In the other conformation (**6b**), bromine would have appreciably deshielded β-methyl as in compound V (**3b**) and the absence of such behaviour supported the conformation **6a**. Deshielding in the methylene resonances ($\Delta\delta$ 0.14) indicated the bromine interaction with the $-CH_2-CH_2-$ linkage and provided an additional evidence for **6a**. Molecular model also showed the conformation **6a** to be sterically favourable.

Compound N-(2′-pyridyl)camphorimide (X) exhibited two resonances (δ 1.07, 3H) and (δ 1.23, 6H) for α-, β- and γ-methyls and the normal resonances for the methine, methylene and pyridyl protons (Table 2). Interaction of sp^2-hybridised lone-pair of nitrogen and imidyl carbonyls in the transition state leads to the restricted rotation and non-planarity about the N-C(pyridyl) bond and the deshielding parameter of β-methyl suggests a preferred conformation (**6a**) for this compound. The spectrum remained unchanged upto 5° which is also in agreement with the preferred conformation. A comparative study of the conformer populations (X, XI, XII) suggests that the effective bulk of the sp^2-hybridised nitrogen lone-pair is smaller than hydrogen atom.

Experimental Procedure

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on Varian A 60 D and Jeol FX 90Q multinuclear spectrometers respectively. IR spectra were recorded in nujol mull on a Perkin Elmer-720 spectrometer. Melting points, chemical analyses and IR bands of the compounds are given in Table 1.

Preparation of compounds I-IX and X-XII

N-aryl(I-IX)- and N-pyridyl(X-XII)-camphorimide derivatives were prepared by heating equimolar amounts of camphoric anhydride and the corresponding aryl- and pyridyl-amines in the presence of anhyd. sodium sulphate at 215-30° for 3-4 hr as reported by Singh *et al.*[17]. The products were extracted with ethanol and recrystallised. All the compounds were purified by fractional crystallization and the purity was checked by TLC.

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Synthesis & Antiarrhythmic Activity of 4-Substituted 2,3-(Tetra/penta/hexa-methylene)quinolines†

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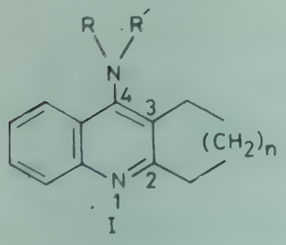
The title compounds **11-39** have been prepared and tested for their antiarrhythmic activity in isolated guinea-pig auricles. Among the compounds **8**, **11-18**, **20**, **21** and **32** which exhibit activity, the potent compound **16** produces effect lasting for a longer duration as compared to **17** in $BaCl_2$-induced arrhythmia in rabbits but both **16** and **17** are found to be less active than quinidine *in vivo* test against aconitine-induced arrhythmia in rats.

The bioexploration[1,2] of 4-aminotetrahydroacridine, 11-amino-7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]-quinoline[3] and their derivatives led to the discovery of a wide spectrum of pharmacological activities[1,4-9] associated with 4-substituted amino-2,3-(polymethylene)quinoline (I) class of compounds. Although N-(N′,N′-diethylaminoethyl)-6,7,8,9,10,11-hexahydrocyclooacta[*b*]quinoline-12-carboxamide[10] (II) is reported to possess antiarrhythmic activity, no such activity is described for I. Therefore, it appeared of



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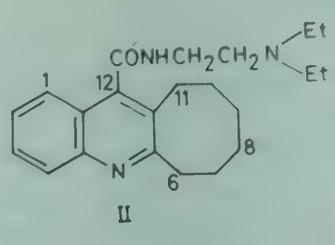


II

interest to examine compounds of the type I for their antiarrhythmic activity. In this paper we report the synthesis of 4-substituted 2,3-(tetra/penta/hexa-methylene)qiinolines (**11-39**) (Table 1) and evaluation of their biological activity.

The synthesis of **11-39** from 4-hydroxy-2,3-(tetra/penta/hexa-methylene)quinolines[11] (**1-3**), the corresponding 4-chloro (**4-6**)[12] and 4-amino (**7-9**)[13] derivatives and 4-chlorocarbonyl-2,3-(pentamethylene)-quinoline (**10**)[14] is outlined in Scheme 1. Reaction of **1**,**2** with alkyl halides and alkylation of **7-9** with appropriate alkyl halides in the presence of NaH afforded 4-(N,N-dialkylaminoalkoxy)quinolines (**11-14**) and 4-substituted amino derivatives (**15-18**, **20-27**, **29** and **30**) respectively. Alternatively, **15-17**, **19-21** and **24-31** were also prepared by the condensation of the 4-chloro compounds (**4-6**) with substituted amines in a steel bomb[1]. The 4-substituted quinolinecarboxamides (**32**, **33**) were obtained by the reaction of **10** with appropriate amines. Condensation of **5**, **6** with substituted phenols gave the 4-substituted phenoxy-quinolines (**34-39**) of which the *p*-nitro product (**36**) was reduced with Raney-Ni and hydrazine hydrate to get *p*-amino derivative (**39**).

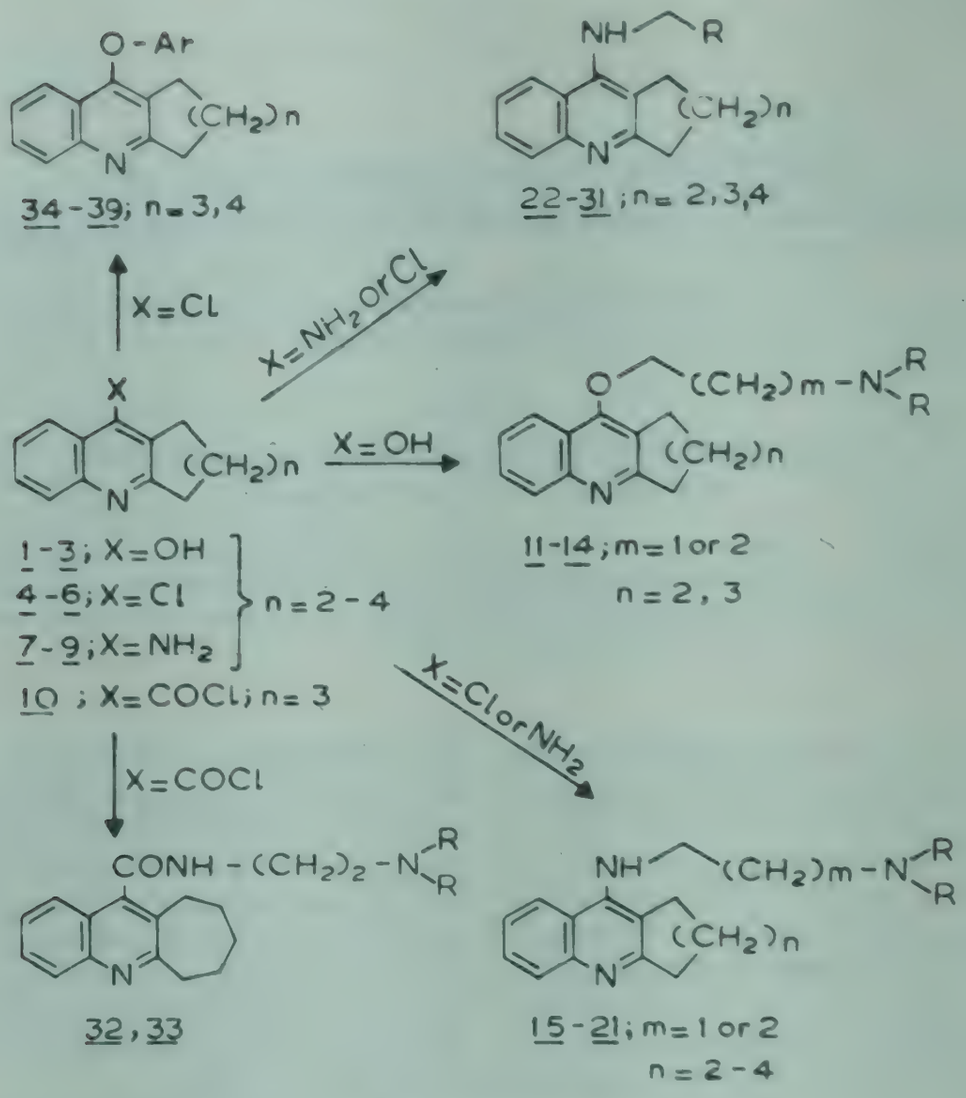
In the mass spectra of 4-alkylamino compounds **22-31**, the most significant peaks at *m/z* 211, 225 and 239 were attributed to the 4-methyleneimino-2,3-(polymethylene)quinoline ($CH_2=\overset{+}{N}H$-heterocyclic ring) fragments resulting from the fission of the side chain. However, in dialkylamino (alkoxy, alkylamino and carboxamido)substituted compounds **11-14**, **15-21**, **32** and **33**, peaks due to methyleniminodialkyl fragments $CH_2=\overset{+}{N}Et_2$ (**86**) and $CH_2=\overset{+}{N}Me_2$ (**58**) were observed.

Biological activity

The antiarrhythmic activity results are given in Tables 2-4. The ALD_{50} values of the compounds **14**, **16** and **17** were found to be 14.7, 46.4 and 68.1 mg/kg i.p. respectively in mice; those of **34-37** were 1000 mg/kg or above and that of compound **38** was 825 mg/kg.

The compounds **8**, **11-18**, **20**, **21** and **32** showed antiarrhythmic activity in the isolated auricle preparation (Table 2). Of these, **15** appeared to be the most active followed by **16** and then **8**, **17** and **18**. The SAR study of these compounds in relation to **15**, based on *in vitro* results, suggests that the pattern of the activity remains unaffected by replacing N atom by oxygen at 4-position of quinoline as in compound **12**

†CDRI Communication No. 3489.



Scheme 1

and also by enlarging size of the hydrogenated ring as in compounds **14** (pentamethylene), **17** (pentamethylene) and **21** (hexamethylene). In general, dimethylamino substituted compounds were found to be comparatively more potent than the corresponding diethylamino analogs irrespective of ring size, e.g. compounds **16** > **17**, **20** > **21** and **11** > **12**. The activity pattern also remained unaffected by increasing the length of the side chain in **11** and **17** giving **13** (4-O-propyl) and **19** (4-N-propyl) respectively. The significant feature of SAR of the side chain was the retention of marked antiarrhythmic activity by complete withdrawal of side chain, e.g. 4-amino-2,3-(pentamethylene)quinoline (**8**).

Although *in vitro* test, **15** was most active but the compounds **8**, **16** and **17** showed more promising profile than **15** *in vivo* testing. In evaluating the effect of most active compounds against aconitine-induced arrhythmia in rats on the onset of early arrhythmia, ventricular tachycardia, ventricular fibrillation and cardiac arrest, the compound **16** was found to be more potent and promising than **17**. Quinidine, the reference compound, was found to be superior to **16** and **17** in this test. However, **16** caused reversal to normal rhythm for longer duration as compared to **17** and quinidine in $BaCl_2$-induced arrhythmia in rabbits. The overall activity data suggested detailed evaluation of compound **16**.

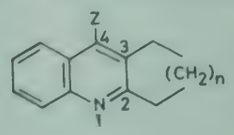
Experimental Procedure

M.ps were taken in a Toshniwal melting point apparatus and are uncorrected. The purity of the compounds was checked on silica gel or alumina TLC plates. IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}), PMR spectra on Perkin-Elmer R-32 and Varian EM-360L instruments using TMS as internal reference (chemical shift in δ, ppm), and mass spectra on a Jeol D-300 instrument fitted with a direct inlet system.

4-(N,N-Dimethylaminoethoxy)-2,3-(tetramethylene)-quinoline (**11**) *Method* (*A*)

To a stirred suspension of NaH (50% dispersion, 1.0 g, 10 mmol) in DMF (10 ml) was added 4-hydroxy-

Table 1—Physical and Analytical Data of 4-Substituted 2,3-(Tetra/penta/hexa-methylene)quinolines



Compd	Z	*n*	Yield (%)	Method	m.p. °C	Crystallized from	Mol. formula	Found (%) (Calc.)		
								C	H	N
11	$O-(CH_2)_2-NMe_2$	2	83	A	Oil*	—	$C_{17}H_{22}N_2O$	75.4 (75.5	8.5 8.2	10.5 10.4)
12	$O-(CH_2)_2-NEt_2$	2	86	A	Oil*	—	$C_{19}H_{26}N_2O$	76.4 (76.5	7.9 7.8	9.4 9.4)
13	$O-(CH_2)_3-NMe_2$	2	74	A	Oil*	—	$C_{18}H_{24}N_2O$	76.3 (76.0	8.7 8.5	10.0 9.9)
14	$O-(CH_2)_2-NMe_2$	3	80	A	165-67	Et_2O-MeOH	$C_{18}H_{24}N_2O.HCl$	67.4 (67.4	7.7 7.9	9.0 8.7)
15	$NH-(CH_2)_2-NEt_2$	2	80	B_1,B_2	Oil*	—	$C_{19}H_{27}N_3$	76.7 (76.7	9.6 9.8	14.3 14.1)
16	$NH-(CH_2)_2-NMe_2$	3	75	B_1,B_2	139-41	Et_2O-MeOH	$C_{18}H_{25}N_3.2HCl$	60.6 (60.3	7.6 8.0	11.8 11.7)
17	$NH-(CH_2)_2-NEt_2$	3	85	B_1,B_2	186-88	Et_2O-MeOH	$C_{20}H_{29}N_3.2HCl$	62.4 (62.2	8.1 8.3	10.9 10.9)
18	$NH-(CH_2)_2-N-C-C_4H_8$	3	59	B_2	Oil*	—	$C_{20}H_{27}N_3$	77.8 (77.6	8.4 8.8	13.7 13.6)
19	$NH-(CH_2)_3-NEt_2$	3	65	B_1	Oil*	—	$C_{21}H_{31}N_3$	77.6 (77.5	9.8 9.6	12.7 12.9)
20	$NH-(CH_2)_2-NMe_2$	4	68	B_1,B_2	Oil*	—	$C_{19}H_{27}N_3$	76.9 (76.7	9.3 9.2	14.4 14.1)
21	$NH-(CH_2)_2-NEt_2$	4	65	B_1,B_2	Oil*	—	$C_{21}H_{31}N_3$	77.2 (77.5	9.4 9.6	12.8 12.9)
22	$NH-CH_2-CH=CH_2$	2	63	B_2	160-62	Et_2O-MeOH	$C_{16}H_{18}N_2.HCl$	69.8 (69.9	6.8 6.7	10.4 10.2)
23	$NH-CH_2-CH=CH_2$	3	73	B_2	190-92	MeOH	$C_{17}H_{20}N_2.HCl$	70.7 (70.7	7.5 7.3	9.8 9.7)
24	$NH-(CH_2)_2-Me$	3	70	B_1,B_2	193-94	Et_2O-MeOH	$C_{17}H_{22}N_2.HCl$	70.4 (70.2	7.9 8.0	9.4 9.6)
25	$NH-(CH_2)_3-Me$	3	84	B_1,B_2	236-37	Et_2O-MeOH	$C_{18}H_{24}N_2.HCl$	70.7 (70.9	7.9 8.3	9.0 9.2)
26	$NH-(CH_2)_4-Me$	3	76	B_1,B_2	178-80	Et_2O-MeOH	$C_{19}H_{26}N_2.HCl$	71.5 (71.6	8.7 8.5	8.3 8.8)
27	$NH-(CH_2)_5-Me$	3	73	B_1,B_2	187-89	Et_2O-MeOH	$C_{20}H_{28}N_2.HCl$	72.5 (72.2	8.7 8.8	8.6 8.4)
28	$NH-(CH_2)_2-CHMe_2$	3	74	B_1	205-7	Et_2O-MeOH	$C_{19}H_{26}N_2.HCl$	71.5 (71.6	8.3 8.5	8.8 8.8)
29	$NH-(CH_2)_2-Me$	4	60	B_1,B_2	190-92	Et_2O-MeOH	$C_{18}H_{24}N_2.HCl$	70.9 (70.9	8.5 8.3	9.3 9.2)
30	$NH-(CH_2)_5-Me$	4	59	B_1,B_2	194-96	Et_2O-MeOH	$C_{21}H_{30}N_2.HCl$	72.9 (72.7	9.3 9.0	8.3 8.1)
31	$NH-(CH_2)_2-CHMe_2$	4	57	B_1	202-4	Et_2O-MeOH	$C_{20}H_{28}N_2.HCl$	72.3 (72.2	8.9 8.8	8.4 8.4)
32	$CONH-(CH_2)_2-NEt_2$	3	91	C	Oil*	—	$C_{21}H_{29}N_3O$	74.4 (74.3	8.6 8.6	12.1 12.4)
33	$CONH-(CH_2)_2-NMe_2$	3	87	C	Oil*	—	$C_{19}H_{25}N_3O$	73.4 (73.3	8.1 8.1	13.6 13.5)
34	OPh	3	86	D	122-24	MeOH	$C_{20}H_{18}NO$	83.5 (83.3	6.3 6.3	4.5 4.9)
35	OPh	4	81	D	130-32	MeOH	$C_{21}H_{30}NO$	83.6 (83.4	6.4 6.7	4.6 4.6)
36	$O-C_6H_4$-*p*-NO_2	4	70	D	146-48	C_6H_6	$C_{21}H_{20}N_2O_3$	72.5 (72.4	5.9 5.8	8.1 8.0)

(Contd.)

Table 1—Physical and Analytical Data of 4-Substituted 2,3-(Tetra, penta hexa-methylene)quinolines—*Contd*

Compd	Z	*n*	Yield (%)	Method	m.p. °C	Crystallized from	Mol. formula	Found (%) (Calc.) C	H	N
37	O–C_6H_4-*p*-COEt	4	90	D	104-6	C_6H_6	$C_{24}H_{25}NO_2$	80.3 (80.2	7.3 7.0	3.7 3.9)
38	O–C_6H_4-*p*-OBzl	4	50	D	91-93	C_6H_6	$C_{28}H_{27}NO_2$	82.4 (82.1	6.5 6.6	3.6 3.4)
39	O–C_6H_4-*p*-NH_2	4	80	E	212-14	C_6H_6	$C_{21}H_{22}N_2O$	79.3 (79.2	6.8 7.0	8.9 8.8)

*The oily products were purified by column chromatography over basic alumina.

Table 2—Effect of Test Compounds on Maximal Driving Frequency of Isolated Guinea-Pig Auricle

Compd	Exp. No.	Concentration (μg/ml)	Mean percentage of inhibition of driving frequency ±SE
8	3	3	24.25±1.4
11	1	3	15.0
12	1	3	5.0
13	1	3	10.0
14	3	3	16.67±4.4
	2	10	24.5
15	2	1	31.0
	3	3	21.0±5.5
	1	10	30.0
16	3	3	27.67±1.45
	1	1	19.5
17	2	1	10.0
	5	3	23.60±3.6
18	3	3	17.67±1.5
	2	10	15.0
20	1	3	10.0
21	1	3	5.0
32	1	3	10.0
Quinidine	4	1	10.1±3.3
	3	3	16.6±3.2

2,3-(tetramethylene)quinoline[11] (**1**; 1.1 g, 5 mmol) and the reaction mixture stirred at 90° for 1 hr under N_2 atmosphere and $Me_2NCH_2CH_2Cl.HCl$ (1.4 g, 5 mmol) in DMF added to it. After stirring further for 3 hr at 90°, the solid was filtered and the filtrate concentrated and extracted with benzene. The extract was washed with water, dried (Na_2SO_4) and concentrated. The oily residue was purified by chromatography on alumina column using benzene as eluant to give **11** as an oil, 1.0 g (83%); PMR ($CDCl_3$): 1.85 [*m*, 4H, $-(CH_2)_2-$], 2.30 [*s*, 6H, $N(CH_3)_2$], 2.66-3.02 (*m*, 6H, C_2-CH_2, C_3-CH_2 and CH_2-N), 4.02 (*t*, 2H, OCH_2, $J=6$ Hz), 7.32-7.52 (*dd*, 2H, C_6-H and C_7-H, $J=9$, 2.5 Hz), 7.90 (*dd*, 1H, C_5-H, $J=9$, 3 Hz), 8.0 (*dd*, 1H, C_8-H, $J=9$, 3 Hz); MS: *m/z* 270 (M^+), 198, 73, 58.

4-(N,N-Diethylaminoethylamino)-2,3-(pentamethylenes)quinoline (**17**) *Method* (B_1)

A mixture of 4-chloro-2,3-(pentamethylene)quinoline[12] (**5**; 1.2 g, 5.1 mmol), $Et_2NCH_2CH_2NH_2$ (0.58 g, 5.1 mmol) and phenol (3.0 g, excess) was heated in a steel bomb at 145-150° for 20 hr, cooled and extracted with benzene. The extract was worked-up as above and chromatographed on alumina column using benzene as eluant to give **17**, 1.4 g (85%), m.p. 186-88°; IR (KBr): 3320 (NH); PMR ($CDCl_3$): 1.60-1.90 [*m*, 6H, $-(CH_2)_3-$], 2.54 [*m*, 6H, $-CH_2-N(CH_2CH_3)_2$], 2.80 (*m*, 2H, C_3-CH_2), 3.0-3.30 (*m*, 4H, C_2-CH_2 and $NHCH_2$); MS: *m/z* 313 (M^+), 312 (M^+-1), 223, 211, 86.

Method (B_2)

Compound **17** was also prepared by the hitherto unkonwn procedure consisting of alkylation of **8**[13] with $Et_2NCH_2CH_2Cl.HCl$ in the presence of NaH-DMF under the conditions as given in method (A) for compound **11**.

N-(N',N'-Diethylaminoethyl)2,3-(pentamethylene)quinoline-4-carboxamide (**32**)

Method (*C*)

To a stirred solution of 4-chlorocarbonyl-2,3-(pentamethylene)quinoline[14] (**10**; 1.2 g, 5 mmol) in thiophene free benzene (15 ml) was added $Et_2NCH_2CH_2NH_2$ (0.58 g, 5 mmol) and the mixture kept for 1 hr and worked-up as described above. The crude oil was purified by chromatography on alumina column using benzene as eluant to give **32** as an oil, 1.5 g, (91%); IR (neat): 3240 (NH), 1800 (CONH); PMR ($CDCl_3$): 0.84 (*t*, 6H, $2\times CH_2-CH_2$, $J=6$ Hz), 1.04-1.92 [*m*, 6H, $-(CH_2)_3-$], 2.44 (*m*, 6H, CH_2N and $2\times CH_2-CH_3$), 2.90 (*m*, 2H, C_3-CH_2-), 3.12 (*m*, 4H, C_2-CH_2 and $CONH-CH_2$); MS: *m/z* 339 (M^+), 340 (M^++1), 223, 86.

4-(p-Nitrophenoxy)-2,3-(hexamethylene)quinoline (**36**)

Method (*D*)

A mixture of **6** (2.0 g, 8 mmol) and *p*-nitrophenol

Table 3—Protective Effect of Compounds **16** and **17** on Aconitine-Induced Arrhythmia in Rats

Compd	Dose (mg/kg i.v.)	Amount of Aconitine (μg/100g) required to produce*			
		EA	VT	VF	CA
16	10	24.6±2.6	33.3±4.3	62.1±6.7	85.1
17	10	18.2±2.2	24.6±3.8	36.3±4.7	66.4±2.1
Saline	—	15.7±2.5	17.5±3.7	47.6±9.6	42.4±7.9
Quinidine	5	52.1±3.6	60.9±2.9	93.6±4.1	120.5±4.2

No of animals used for each compound = 5.

*EA = Early arrhythmia, VT = Ventricular tachycardia, VF = Ventricular fibrillation, CA = Cardiac arrest, Values are mean ±SE.

(4.0 g, 20 mmol) was heated in a steel bomb at 140° for 24 hr, cooled and extracted with benzene. The extract was washed with NaOH solution, dried (Na_2SO_4), concentrated and the oily residue crystallised from hexane to give **36** 2.0 g, (70%), m.p. 146-48°; PMR ($CDCl_3$). 1.10-1.92 [*m*, 8H, $-(CH_2)_4-$], 2.75 (*m*, 2H, C_3-CH_2-), 3.08 (*t*, 2H, C_2-CH_2-, $J=6$ Hz), 6.68 (*d*, 2H, Ar-*H o* to NO_2, $J=9$ Hz); MS: *m/z* 348 (M^+), 349 ($M^+ + 1$), 319, 222, 198, 197, 184.

4-(*p-Aminophenoxy*)-2,3-(*hexamethylene*)*quinoline* (**39**)

Method (*E*)

To a mixture of **36** (0.7 g, 2 mmol) and Raney-Ni (0.1 g) in EtOH (10 ml) was added $NH_2NH_2.H_2O$ (2 ml) dropwise and the mixture heated on a water-bath for 15 min, concentrated under reduced pressure and the residue extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and concentrated to get **39**, 0.5 g (80%), m.p. 212-14°; IR (KBr): 3480, 3360 (NH); PMR ($CDCl_3$): 2.84 (*t*, 2H, C_3-CH_2-, $J=6$ Hz), 3.10 (*t*, 2H, C_2-CH_2-, $J=6$ Hz), 6.52 (*m*, 4H, Ar-*H o* to NH_2 and N*H*$_2$), 7.24 (*dd*, 2H, Ar-*H m* to NH_2, $J=9$ and 2.5 Hz); MS: *m/z* 318 (M^+).

Pharmacological methods

The approximate dose which killed 50% of animals (ALD_{50}) were calculated according to the method of Horn[15]. The acute toxicity study and gross behavioural observations were carried out in mice (20-25 g) by i.p. administration of graded doses of compounds using five animals at each dose. The effect on blood pressure, respiration and interaction with acetylcholine and epinephrine were studied in anaesthetised (pentobarbitone, 35 mg/kg i.v.) cats.

The *in vitro* antiarrhythmic activity of these compounds was tested by the method of Dawes[16] in isolated guinea-pig auricle at 1, 3 and 10 μg/ml concentrations. The antiarrhythmic effect at each concentration was calculated as % reduction of maximal rate of stimulation using quinidine as a reference standard. The *in vivo* activity was studied in anaesthetised (urethane, 1.5 mg/kg i.p.) male rats weighing between 100 and 150 g. The jugular vein was cannulated for infusion of aconitine (100 μg/ml, 4.15 μg/min) by slow injection apparatus. The ECG changes were monitored and recorded on an encardiorite polygraph before and after the addition of test compound and during the infusion of aconitine according to the procedure described by Junien *et al.*[17]. The test compounds were injected 2 min before starting the infusion. Results are given in Table 3 and are expressed as the amount of aconitine required for the onset of early arrhythmia, ventricular tachycardia, ventricular fibrillation and cardiac arrest per 100 g of body weight.

The compounds found active *in vivo* test were further tested with $BaCl_2$-induced arrhythmia in conscious rabbits according to the methods described by Szeker and Papp[18]. Ventricular arrhythmia was elicited by a slow i.v. injection of 2% $BaCl_2$ into the marginal ear vein.

Table 4—Effect of Compounds **16** and **17** on $BaCl_2$-Induced Arrhythmia in Rabbits

Compd	No. of rabbits	dose (mg/kg i.v.)	Amount of $BaCl_2$ injected to elicit arrhythmia	Reversal to normal rhythm and duration (min)
16	2	10	2	12
17	2	10	8	5.5
Quinidine	—	5	9.6	4

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Notes

A Simple Procedure for Preparation of α-Diazocarbonyl Compounds

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The use of 1,8-diazabicyclo[5.4.0]undec-7-ene as a base in Regitz reaction leads to improved yields of α-diazocarbonyl compounds in much shorter time (15 min.).

The reaction of active methylene compounds and α-formylated ketones with *p*-toluenesulfonyl azide and a base to give α-diazocarbonyl compounds (Eqs. 1 and 2) has been studied extensively by Regitz and other workers[1,2].

(1)

(EWG = electron withdrawing group)

(2)

In most instances, triethylamine or diethylamine is used as the base. Modifications of the Regitz reaction include the use of potassium ethanolate/ethanol[3] and phase transfer catalysed method[4,5]. While the Regitz reaction is fairly general, it fails with sterically hindered ketones and this difficulty has been overcome by Mander through the use of the more reactive 2,4,6-triisopropylbenzenesulfonyl azide in conjunction with a mixture of tetra-*n*-butylammonium bromide and 18-crown-6 as a catalyst and potassium hydroxide as the base[6].

An ongoing synthetic programme in our laboratory necessitated the preparation of 5-diazo-6,7-dihydro-2,6,6-trimethyl-4(5*H*)-benzofuranone (**2**). Reaction of 6,7-dihydro-5-formyl-2,6,6-trimethyl-4(5*H*)-benzofuranone (**1**) under the usual Regitz reaction conditions with *p*-toluenesulphonyl azide and triethylamine was very slow and did not go to completion even after 24 hr at 30°C. As **1** is a sterically hindered ketone, Mander's conditions were applied. Even this attempt was found to be unsuccessful. A systematic investigation of the reaction of **1** and *p*-toluenesulphonyl azide with various bases was, therefore, undertaken. While bases like diisopropylethylamine and 4-dimethylaminopyridine (DMAP) were not useful, the reaction of **1** proceeded moderately well in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO) to give the required **2** in 56% yield after 1 hr at 30°C. Encouraged by this result, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as the base. A dramatic improvement in yield (100%) and reduction in reaction time (15 min) was observed. In order to examine the generality of the reaction, a few other substrates shown in the Table 1 were reacted with *p*-toluenesulphonyl azide and DBU. The yields of the diazo compounds obtained by this procedure (see Table 1) are either as good or superior to the ones reported earlier. Since the procedure is very simple and the yields uniformyl good, this modification of the Regitz reaction should find widespread use in organic synthesis.

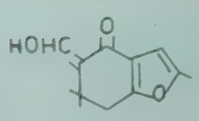
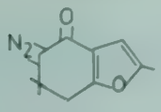
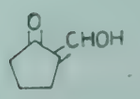
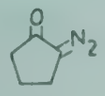
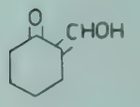
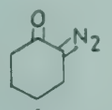
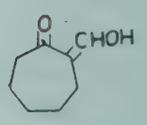
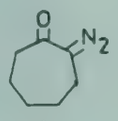
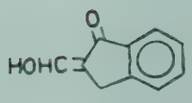
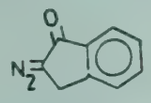
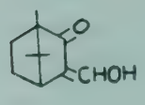
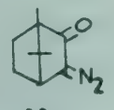
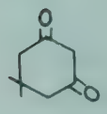
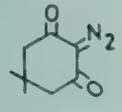
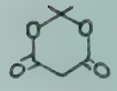
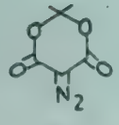
5-Diazo-6,7-dihydro-2,6,6-trimethyl-4(5H)-benzofuranone (**2**)

To a stirred solution of **1** (3.76 mmol) in dichloromethane (5 ml) was added *p*-toluenesulphonyl azide (3.76 mmol) in dichloromethane (5 ml) followed by DBU (0.857 g, 5.64 mmol). The mixture was stirred for 15 min at 30°C, poured into 10% aq. potassium hydroxide (20 ml), the organic layer separated, washed once with dil hydrochloric acid and thrice with water, dried ($MgSO_4$) and evaporated to give **2** (0.765g, 100%) m.p. (hexane) 102-3° (decomposes slowly at room temperature); IR (KBr): 2100, 1660 and 1420 cm^{-1}; PMR ($CDCl_3$/TMS): δ 1.38 (*s*, 6H), 2.30 (*s*, 3H), 2.82 (*s*, 2H), 6.27 (*s*, 1H); MS (*m/z*); 204 (M^+) (Found: C, 65.5; H, 6.4; N, 14.3. $C_{11}H_{12}N_2O_2$ requires C, 64.7; H, 5.9; 13.7%)

The same procedure was applied for the preparation of other diazo compounds (Table 1). All the reactions (2 mmol scale) were over in less than 5 min as evidenced by the appearance of a yellow colour due to the diazo compound. However, the reactions were allowed to proceed for 15 min at 30°C except in the case of substrates **3** and **21** (0°C, 15 min) and **11** (30°C, 25 min). Physical data of all the products obtained are given in the Table 1.

We thank Dr S Chandrasekharan (Indian Institute of Technology, Kanpur) for kindly recording the mass spectra and one of us (YKR) is grateful to the CSIR, New Delhi for financial assistance. This work is supported in part by the Special Assistance Programme of the UGC, New Delhi.

Table 1 - Physical Data of Various α-Diazocarbonyl Compounds Synthesised.

Substrate	Product	Yield(%) Obs.[a]	Rep.	b.p./m.p.(°C)[b]	Ref.
 1	 2	100	--	102-3	-
 3	 4	81(82)	98	60-65/2mm[c] (34-37/0.8mm)	1
 5	 6	95(100)	82	65/0.3mm[c] (50/0.3mm)	1
 7	 8	94(100)	83	75/0.2mm[c] (62/0.4mm)	1
 9	 10	73	58[d]	85-86(86-88)	7
 11	 12	74	74	74-75(74-75)	2
 13	 14	96	78	107-8(106-8)	2
 15	 16	76	47[e]	90-91(92-93)	10
$CH_2(CO_2CH_3)_2$ 17	$N_2C(CO_2CH_3)_2$ 18	79(81)	42	60/0.2mm[c] (45/0.2mm)	11
$CH_2(COC_6H_5)_2$ 19	$N_2C(COC_6H_5)_2$ 20	82	81	104-5(107)	8
$CH_2(SO_2C_6H_5)_2$ 21	$N_2C(SO_2C_6H_5)_2$ 22	95	70	99(oo)	9
$CH_2COCH_2CO_2Et$ 23	$CH_3COCN_2CO_2Et$ 24	81(82)	80	85/0.2mm[c] (84-85/5mm)	2

(a) Yields obtained after purification by column chromatography are given in parentheses; (b) Literature b.p./m.p. are given in parentheses; (c) bath temperature; (d) synthesized by Forster reaction; and (e) synthesized by amine diazotization.

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Reported New Syntheses of 5,6-Dihydro-6,11-dioxomorphanthridine & 5,6-Dihydro-6-oxomorphanthridine cannot be Repeated

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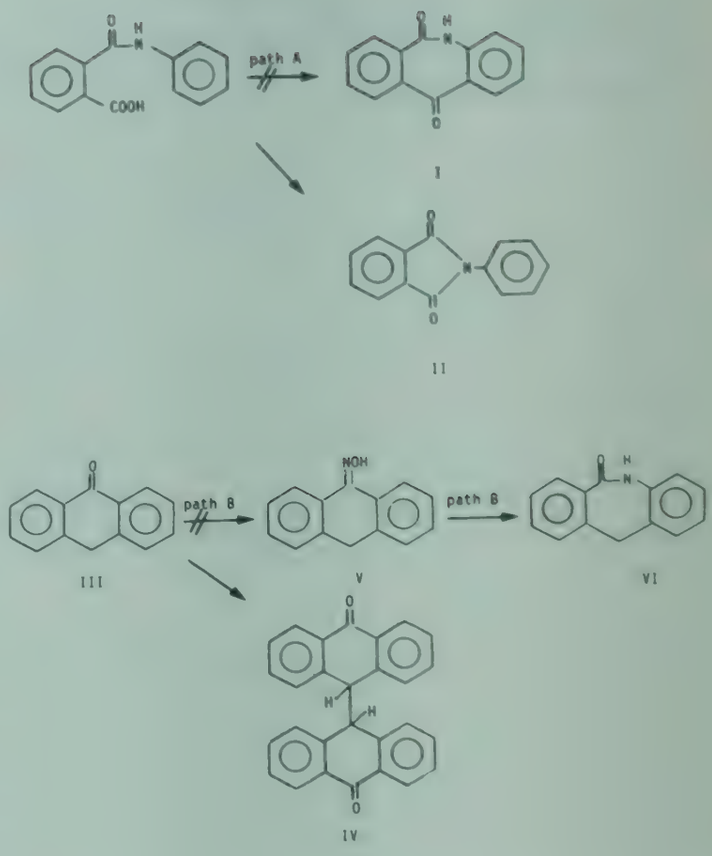
Two new procedures for the synthesis of 5,6-dihydro-6,11-dioxomorphanthridine (I) and the corresponding 11-deoxo derivative (VI) [see *Indian J Chem*, **23B** (1984) 85, 165] are in error and do not give these compounds. Instead these procedures lead to N-phenylphthalimide (II) and a 10,10′-bianthrone derivative (IV) respectively.

While we are aware that experimenting always encompasses some risk of error, we deem it necessary to correct a couple of reports by Sinha *et al.*[1,2]. These authors have recently reported in two separate notes[1,2] published in this Journal, two new procedures for the synthesis of 5,6-dihydro-6,11-dioxomorphanthridine (I) and the corresponding 11-deoxo derivative (VI) according to the respective paths A and B (see Scheme 1).

In our hands, repeated attempts to reproduce the first reaction[1] (path A) have led only to compound (II). This compound was isolated in pure form (73% yield) and identified as N-phenylphthalimide (II) by analytical and spectral data and by comparison with an authentic sample prepared by a knwon method[3]; m.p. 206° (lit.[3] 208°); TLC (EtOAc/toluene, 3:7): $R_f \simeq 0.8$; IR (nujol): 1780, 1720 cm^{-1} (C=O); PMR ($CDCl_3$): δ 7.68-8.00 (4 H, *m*), 7.44 (5 H, *s*); MS: *m/z* 224 $(M+H)^+$, 133, 105 (Found: C, 75.2; H, 4.0; N, 6.23. Calc. for $C_{14}H_9NO_2$; C, 75.3; H, 4.1; N, 6.3%).

Analogously, the only product isolated from the second reaction[2] (path B) carried out following the procedure of Sinha *et al.*[2], was the compound (IV) a 10,10′-bianthrone, instead of the anthrone oxime (V).

Failure to obtain V may be explained by the low carbonyl character of the keto group of anthrone (III) which is in tautomeric equilibrium with the corresponding anthranol[4].



Compound (IV) was isolated in 70% yield and identified on the basis of analytical and spectral data; m.p. 252° (lit.[5] 256°); TLC ($EtOAc/CH_2Cl_2$, 2:1); $R_f \simeq 0.2$; IR (nujol): 1660 cm^{-1} (C=O); PMR (DMSO + $CDCl_3$): δ 7.77 (4H, *m*), 7.37-7.49 (8H, *m*), 6.99 (4H, *m*), 4.97 (2H, *s*, aliphatic protons); MS (Cl, CH_4): *m/z* 387 $(M+H)^+$, 235, 223, 195 (Found: C, 86.8; H, 4.7. Calc. for $C_{28}H_{18}O_2$: C, 87.0; H, 4.7%).

Compounds I and VI can instead be conveniently prepared by ring expansion of anthraquinone according to Schmidt reaction[6] and by cyclization of 2-benzyl-phenylisocyanate[7], respectively.

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Displacement Reactions of 2,3-Dichloro-6-nitroquinoxaline: Synthesis of s-Triazolo[3,4-*a*]quinoxaline†

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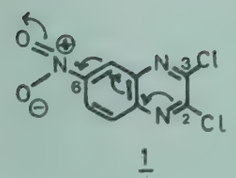
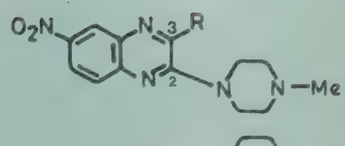
2,3-Dichloro-6-nitroquinoxaline (**1**) undergoes displacement reactions with 1-methylpiperazine in the hot to give the bis-derivative (**2**) and at 30°C selectively at position-2 to afford the mono-derivative (**3**). Structure-proof for the latter involves transformation of **3** through hydrazine derivative (**4**) to the traizoloquinoxaline (**5**) and its 1-phenyl derivative (**6**) and comparison of the chemical shifts of protons at C-9 in the pair.

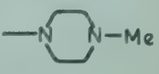
In the course of our ongoing programme[1] to develop new amoebicides and discovery[2] of this activity in a series of condensed quinoxalines, we were attracted by a literature claim[3] of pronounced antiamoebic activity for 6-N,N-dimethylformamidino-2,3-*bis*-N-methyl-piperazinoquinoxaline. We synthesised this by the reported procedure and found it to be inactive in our test systems. During this process, we observed that an early precursor, 2,3-dichloro-6-nitroquinoxaline (**1**) underwent selective displacement of one of the two reactive chlorine atoms to afford the product (**3**). We explored this finding to synthesize several new derivatives for biological evaluation. Further, by a series of manipulations ending with the triazolo-quinoxalines (**5**) and (**6**), we were able to provide convincing structure proof for product (**3**).

The hydrazine derivative **4**, obtained from **3** by treatment with hydrazine, was transformed to **5** and **6**, respectively by reaction with triethyl orthoformate and benzoyl chloride. In the 90 MHz PMR spectrum of **5**, the C_9-H signal appeared at 8.95 as a doublet ($J=2$ Hz; coupling with *meta*-placed C_7-H). The same signal in **6** appeared upfield at 8.20 while there were only minor differences in the location of other proton signals. The upfield shift is to be attributed to the shielding influence of the phenyl group at position-1 in **6**, which is twisted out of plane. If the monodisplacement product of **1** had the alternative structure (substituents at C-2 and C-3 are reversed in **3**), the resultant triazoles would be **7** and **8**. The signal due to



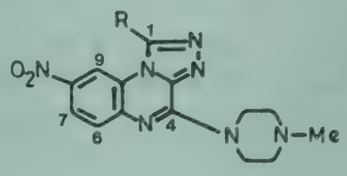
1



2 R = 

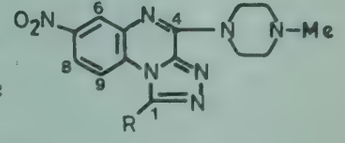
3 R = Cl

4 R = $NH.NH_2$



5 R = H

6 R = C_6H_5



7 R = H

8 R = C_6H_5

C_9-H would have suffered an upfield movement going from **7** to **8** and this would be a doublet with a large *ortho* coupling (8 Hz). The structure of **3** and of all resultant products are thus secured. It is to be noted that this result would have been expected from electronic considerations as well. The arrows on **1** would require C-2 to be more electrophilic than C-3.

All melting points are uncorrected. PMR spectra were recorded in $CDCl_3$ on a Varian A 60 or Brucker WH 90 NMR spectrometer and mass spectra on a Varian Mat CH 7 spectrometer.

2,3-Bis(4-methyl-1-piperazinyl)-6-nitroquinoxaline (**2**)

A mixture of **1** (16 g) and N-methylpiperazine (20 g) in 2-methoxyethanol (150 ml) was stirred and heated under reflux for 16 hr. The mixture was then cooled in an ice-salt bath and filtered. The filtrate was evaporated *in vacuo* and the residue triturated with water and filtered. The product was crystallised from methylene chloride-ether to give **2** (14 g), m.p. 216-18° (Found: C, 58.1; H, 6.9; N, 26.1. $C_{18}H_{25}N_7O_2$ requires C, 58.2; H, 6.8; N, 26.4%), PMR: δ 2.37 ($N-CH_3$, *s*), 2.4-2.7 ($CH_2-N(CH_3)-CH_2$, t), 3.5-3.9 ($CH_2-N(Ar)-CH_2$, 2 overlapping *t*), 7.68 (C-8 *H*; *d*, $J=10$ Hz), 8.17 (C-7 *H*, *dd*, $J=10$, 2.5 Hz), 8.55 (C-5 *H*, *d*, $J=2.5$ Hz).

3-Chloro-2-(4-Methyl-1-piperazinyl)-6-nitroquinoxaline (**3**)

A solution of **1** (13.4 g) in methylene chloride (150 ml) was stirred at room temperature (30°C) and

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treated dropwise with 1-methylpiperazine (11 g). After being left overnight, the solvent was evaporated off. The residue was triturated with water and filtered. The product was crystallised from methylene chloride-hexane to give **3** (12.5 g) m.p. 128-30° (Found: C, 50.9; H, 4.7; N, 22.9. $C_{13}H_{14}ClN_5O_2$ requires C, 50.7; H, 4.6; N, 22.8%); MS: M^+ (^{35}Cl) 307, (^{37}Cl) 309; PMR: δ 2.37 ($N-CH_3$, *s*), 2.60 ($CH_2-N(CH_3)-CH_2$; *t*), 3.77 ($CH_2-N(Ar)-CH_2$), 7.77 (C-8 *H*, *d*, $J=10$ Hz); 8.33 (C-7 *H*, *dd*, $J=10$, 2.5 Hz), 8.63 (C-5 *H*, $J=2.5$ Hz).

3-*Hydrazino*-2-(4-*methyl*-1-*piperazinyl*)-6-*nitroquinoxaline* (**4**)

Compound (**3**, 5 g) hydrazine hydrate (6 g) and ethanol (100 ml) were refluxed on a water-bath for 2 hr. A dark yellow crystalline solid separated from the reaction mixture on cooling. This was filtered off and the residue (3 g) recrystallised from chloroform to give **4**, m.p. 245° (Found: C, 51.2; H, 5.8. $C_{13}H_{17}N_7O_2$ requires C, 51.5; H, 5.7%).

4-(4-*Methyl*-1-*piperazinyl*)-8-*nitro*-*s*-*triazolo*[3,4-*a*]*quinoxaline* (**5**)

Compound (**4**, 0.6 g) and triethyl orthoformate (5 ml) were heated at 120-40° under reflux for 4 hr. The solid that separated was filtered off and recrystallised from methanol (0.2 g, m.p. 225°) (Found: C, 53.5; H, 5.2. $C_{14}H_{15}N_7O_2$ requires C, 53.7; H, 4.9%); MS: M^+ at *m/z* 313; PMR: δ 2.32 ($N-CH_3$, *s*) 2.57 [$CH_2-N(CH_3)-CH_2$, *m*], 4.43 [$Ar-N(CH_2)_2$, *m*), 7.40 (C-6 *H*, *d*, $J=8$ Hz), 8.07 (C-7 *H*, *dd*, $J=2$, 8 Hz), 8.95 (C-9 *H*, *d*, $J=2$ Hz), 10.07 (C-1 *H*, *s*).

1-*Phenyl*-4-(4-*methyl*-1-*piperazinyl*)-8-*nitro*-*s*-*triazolo*[3,4-*a*]*quinoxaline* (**6**)

Compound (**4**, 0.6 g) was added with stirring to a well-cooled solution of pyridine (6 ml) admixed with benzoyl chloride (0.3 g). The mixture was warmed on a steambath until it was clear, heated under reflux at 100° for 1 hr, cooled, poured over crushed ice and left overnight. The solid that separated was filtered off, washed with water and crystallised from methanol to yield **6** (0.4 g) m.p. 195° (Found: C, 61.1; H, 5.1. $C_{20}H_{19}N_7O_2$ requires C, 61.6; H, 4.9); PMR: δ 2.40 ($N-CH_3$, *s*), 2.67 [$CH_2-N(CH_3)-CH_2$, *m*], 4.62 [$Ar-N(CH_2)_2$, *m*], 7.22 (C-6 *H*, *d*, $J=8$ Hz), 8.17 (C-7 *H*, *dd*, $J=2$, 8 Hz), 8.20 (C-9 *H*, *d*, $J=2$ Hz), 7.70 (C_6H_5 at C-1).

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Amine-induced Photodehalogenation of Photoisomers of Aldrin, Dieldrin & Endrin†

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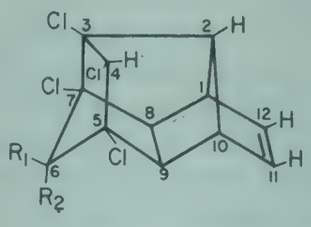
Photolysis of toxic photoisomers, viz. photoaldrin, photodieldrin and photoendrin of the corresponding cyclodiene insecticides aldrin, dieldrin and endrin in the presence of triethylamine gives products arising by the loss of chlorine atom(s) from the geminal bridge. The structures and stereochemistry of the new metabolites are discussed.

The cyclodiene insecticides like aldrin, dieldrin and endrin have acquired notoriety for their environmental stability and their propensity to give a large number of transformation products by both biotic and abiotic agents. Amongst the abiotic factors, light induced transformation products have assumed some importance as some of these are more toxic than the parent insecticides. In an earlier communication from this laboratory it was reported that triethylamine-induced photodehalogenation of cyclodienes yielded products by stereoselective loss of *syn*-chlorine atom from the geminal bridge carbon atom. The title investigation is an extension of this work to the toxic photoisomers of cyclodiene insecticides. Some new photometabolites have been isolated and their structures elucidated.

Photoaldrin (**1**) (3-*exo*,4,5,6,6,7-hexachloro-pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{5,9}]dodeca-$\Delta^{11(12)}$-ene)[2], prepared by the method of Rosen and Carey[3] (500 mg), in dry and distilled triethylamine (25 ml) was irradiated for 6 hr using a high pressure Hg lamp, and pyrex filter at room temperature. The reaction appeared to be almost complete (≈90% GLC). The mixture was diluted with ether (200 ml) and extracted with dil HCl to remove triethylamine. The ether extract washed with water, dried and solvent removed to furnish a residue (350 mg), which was chromatographed on a column of silica gel (25 g), eluting the column in succession with (i) hexane to yield **2** (200 mg), (ii) hexane-benzene (9:1) to yield unreacted **1** (20 mg) and (iii) hexane-benzene (7:3), to yield the second dechlorinated product **3** (40 mg).

The new photometabolite (**2**), crystallised from methanol as colourless plates, m.p. 90-92° (Found: C, 43.8; H, 3.1. $C_{12}H_9Cl_5$ requires C, 44.0; H, 2.7%). The molecular ion peak at *m/z* 328 in its mass spectrum indicated its formation from **1** via the loss of one chlorine atom. The presence of a strong peak at *m/z* 65 due to $C_5H_5^+$ (formed by retro Diels-Alder fragmentation) showed that in **2** the skeleton of **1** is intact. In comparison to parent (**1**), its PMR spectrum [($CDCl_3$): δ 6.18 (2H, *m*, H_{11} & H_{12}), 5.0 (1H, *s*, H_4), 4.62 (1H, *s*, H_6), 3.40 (1H, *s*, H_1), 3.20 (1H, *s*, H_{10}), 3.00 (1H, *s*, H_8), 2.90 (1H, *s*, H_9), 2.55 (1H, *s*, H_2)] displayed an additional one-proton singlet at δ 4.62, indicating that the chlorine atom has been lost from the geminal carbon atom C-6. The *anti*-chloro orientation of **2** is based on the fact that **2** was also obtained by acetone-



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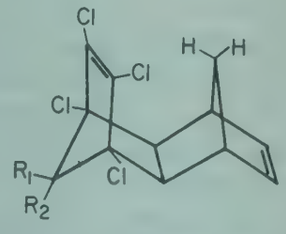
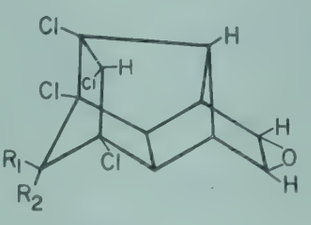
2, $R_1 = H; R_2 = Cl$
3, $R_1 = Cl; R_2 = H$



4, $R_1 = H; R_2 = Cl$
5, $R_1 = Cl; R_2 = H$



6, $R_1 = R_2 = Cl$
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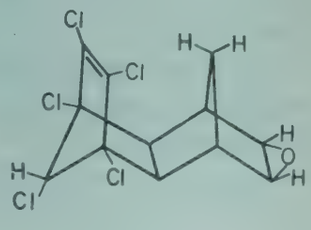

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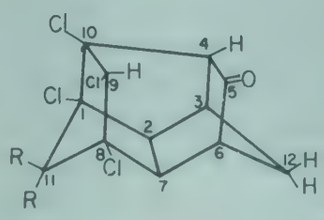
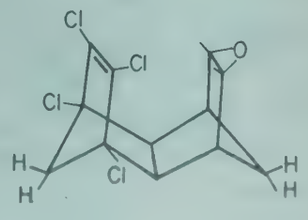


9; R = Cl
10; R = H



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†Contribution No. 301 from the Division of Agr. Chemicals, IARI.

sensitized mild photo-irradiation of **4** which also has been shown to have[4] *anti*-chloro orientation.

The second new metabolite (**3**) crystallised from benzene-hexane as colourless prisms, m.p. 138-42° (Found: C, 43.50; H, 3.03. $C_{12}H_9Cl_5$ requires C, 43.95; H, 2.7%). Its mass spectrum (M^+; *m/z* 328) indicated that it was isomeric with **2**. In the PMR spectrum of **3** [($CDCl_3$): δ 6.20 (2H, *m*, H_{11} & H_{12}), 4.98 (1H, *s*, H_4), 4.80 (1H, *s*, H_6), 3.52 (1H, *s*, H_1), 3.40 (1H, *s*, H_{10}), 3.20 (1H, *s*, H_8), 2.90 (1H, *s*, H_9), 2.40 (1H, *s*, H_2)], the one-proton singlet at δ 4.80, assignable to *H*CCl, indicated that **3** is formed by the loss of one of chlorine atoms from C-6. Since **2** was assigned *anti*-chloro orientation at C-6, the isomeric **3** must have *syn*-chloro orientation at C-6. This was further confirmed by obtaining **3** during acetone-sensitized photo-irradiation of **5**, which is known to have *syn*-chloro orientation[1].

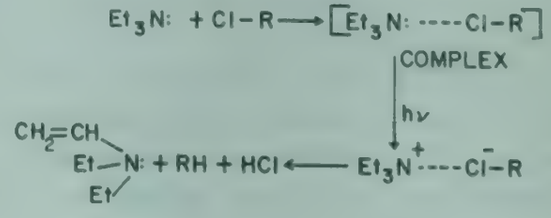
Photodieldrin[5] (**6**, 500 mg) (3-exo,4,5,6,6,7-hexachloro-11,12-exo-epoxypentacyclo-[6.4.0.$0^{2,10}$.$0^{3,7}$.$0^{5,9}$]dodecane)[2] on irradiation in triethylamine (50 ml) under the same conditions appeared to change completely in 12 hr (GLC). Work-up as above gave a single product **7** (400 mg) which crystallised from hexane-benzene as colourless needles, m.p. 172-75° (Found: C, 41.5; H, 2.7. $C_{12}H_9Cl_5O$ requires C, 41.6; H, 2.6%). Compound (**7**, M^+ *m/z* 344) appears to arise from **6** via the loss of one chlorine atom. The presence of a strong peak in the mass spectrum of **7** at *m/z* 81 due to $C_5H_5O^+$ ion indicated that in the formation of **7** no rearrangement has taken place. In comparison to parent **6**, the PMR spectrum of **7** [($CDCl_3$): δ 4.90 (1H, *s*, H_4), 4.65 (1H, *s*, H_6), 3.50 (1H, *s*, H_{11}), 3.30 (1H, *s*, H_{12}), 3.20 (1H, *s*, H_8), 3.10 (1H, *s*, H_9), 3.01 (1H, *s*, H_1), 2.78 (1H, *s*, H_{10}), 2.54 (1H, *s*, H_2) displayed a new one-proton singlet at δ 4.65 due to *syn*-proton at C-6. The *anti*-chloro orientation of C-6 in **7** is again based on the fact the **8** having similar orientation of the Cl atom[4] could be readily transformed to **7** by acetone-sensitized phototransformation.

Photoendrin[6] (**9**, 200 mg) (1,8-exo,9,10,11,11-hexachloropentacyclo[6.2.1.$1^{3,6}$.$0^{2,7}$.$0^{4,10}$]dodecan-5-one)[2], on similar irradiation in triethylamine (20 ml) for 10 hr, gave a new metabolite (**10**) which crystallised from methanol as colourless cubes, m.p. 169-70° (Found: C, 45.8; H, 3.5. $C_{12}H_{10}ClO$ requires C, 45.9; H, 3.2%). Its mass spectrum (M^+, *m/z* 310) indicated that **10** is formed from **9** via the loss of two chlorine atoms. However, its carbonyl absorption at 1780 cm^{-1} (nujol) indicated its skeletal similarity with **9**. The PMR spectrum of **10** [($CDCl_3$): 4.80 (1H, *s*, H_9), 3.40 (1H, *s*, H_2) 3.38 (1H, *s*, H_7), 3.30 (1H, *s*, H_3) 3.20 (1H, *d*, J = 12 Hz, H_{12})] when compared with that of **9** showed a new two-proton doublet at δ 2.85. This doublet is due to the two new protons in place of the two chlorine atoms lost from geminal carbon C-6. Structure (**10**) was further confirmed when **11** synthesised earlier[1] by un-ambiguous route, gave **10** on photolysis under sensitized condition. Hence unlike **1** and **6**. photoendrin(**9**) looses both the chlorine atoms at C-6 on photodehalogenation.

Thus, the amine-induced photodehalogenation, which proceeds in a stereoselective manner in the cyclodienes takes a different course in the case of their photoisomers each giving a different product or mixture by loss of Cl atom from the geminal bridge.

Amine-induced photodehalogenation of haloalkyl compounds including halogenated cyclodienes is known to proceed through the formation of charge transfer (CT) complexes[7,8]. In the present case **1**, **6** and **9** also from CT complex with triethylamine as seen by the appearance of a new broad absorption band above 290 nm in the UV spectra of these compounds in hexane in the presence of triethylamine.

The mechanism of amine-induced photoreduction of haloalkyl compounds proposed by Stevenson and Coppinger[8] and applied in the present case is shown in Scheme 1.



R = Residual Structure of
1, 6 and 9

SCHEME 1

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Photolysis of Mandelic Acid, Benzhydrol & Benzoin in Presence of Ferric Chloride & Cupric Chloride

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Irradiation of mandelic acid, benzhydrol and benzoin in the presence of ferric chloride/cupric chloride in water, dichloromethane and acetonitrile media has been investigated and the products obtained identified. In the presence of ferric chloride these substrates give benzophenone; 1,1,1',1'-tetraphenyldimethyl ether, benzophenone; and benzil, respectively. Similar products have been obtained with cupric chloride albeit in lower yields.

Balsells *et al.*[1] have reported the photochemistry of alcohols leading to ethers as the major products and the ketones in minor quantities. In view of the above report our attention was directed towards the use of the Lewis acids, i.e. metallic salts in the light-induced oxidation of α-hydroxy acid (mandelic acid), secondary alcohol (benzhydrol) and α-keto alcohol (benzoin).

Mandelic acid (I)[2] did not undergo any reaction in the dark in the presence of ferric chloride in aqueous solution or cupric chloride in acetonitrile. However, when I was irradiated with 125 watt high pressure mercury vapour lamp in a pyrex reactor in the presence of aqueous ferric chloride for 3 hr†, benzaldehyde (II) was obtained in 6.4% yield and 90% mandelic acid was recovered unchanged. Some tarry material was also obtained which could not be identified.

Phtolysis of I in the presence of cupric chloride resulted in the formation of II in 5.2% yield, phenylglyoxalic acid (III) as a white solid in 1.8% yield. An unidentified yellow coloured sticky product was also obtained in 3.6% yield.

Diphenylcarbinol, ($C_6H_5.CHOH.C_6H_5$, IV) did not undergo any reaction in dark with ferric chloride in dichloromethane or cupric chloride in acetonitrile solution but when kept in the diffused sunlight in the presence of ferric chloride in dichloromethane for 48 hr, only 25% of the starting material was consumed and this amount did not increase with increase in irradiation period. However, IV on irradiation with a 125 watt high pressure mercury vapour lamp in the presence of ferric chloride in dichloromethane for 10 min gave the ether $(C_6H_5)_2CH-O-CH(C_6H_5)_2$ (V) in 49% yield which was characterised by its 90 MHz NMR spectrum. Balsells *et al.*[1] reported 94% yield of V in the absence of a catalyst after irradiation for 18 hr. Besides, the ether (V), benzophenone (VI) was obtained in 33.0% yield in addition to an unidentified product in 2.7% yield, unreacted benzylhydrol in 5.4% yield and an unidentified tar in 5.3% yield.

Benzhydrol (IV) when kept in diffused sunlight in the presence of cupric chloride in acetonitrile for 24 hr, only 10% of the starting material underwent reaction. However, IV when irradiated with a 125 watt UV lamp for 3 hr in the presence of cupric chloride in acetonitrile afforded the ether (V) in 43.7% yield and VI in 35.8% yield. Unreacted benzhydrol was recovered in 5.5% yield and rest of the residue was an unidentified tar.

Benzoin ($C_6H_5CO.CHOHC_6H_5$, VII) gave benzil ($C_6H_5CO.CO.C_6H_5$, VIII, 1%) when kept in diffused light for 3 hr in the presence of ferric chloride in dichloromethane. This quantity did not increase even after 48 hr. However, VII on irradiation as in the case of I and IV, in the presence of ferric chloride in dichloromethane for 3 hr furnished VIII in 52.4% yield and unreacted benzoin in 33% yield. A reddish brown polymeric compound was also obtained in 9.4% yield.

Benzoin (VII) did not undergo any reaction when kept in diffused sunlight in the presence of cupric chloride in acetonitrile for 3 hr. However, on irradiation of VII by UV light for 3 hr, in the presence of cupric chloride, benzaldehyde (II, 4.3%), benzil (VIII, 23.8%), benzoic acid (IX, 8.2%) and unreacted benzoin (28.8%) were obtained. Two other reddish brown coloured products were obtained which could not be identified.

The formation of oxidation products can be rationalised as follows: The catalysts release a chlorine radical as a result of irradiation which abstracts hydrogen thereby providing carbonyl compounds. Fe^{3+} is reduced to Fe^{2+} and Cu^{2+} is reduced to Cu^{+}. This suggestion is substantiated by formation of phenylglyoxalic acid (III) as well as benzophenone (VI) from mandelic acid and benzhydrol, respectively. The formation of ether (V) may be the result of a parallel reaction, as reported by Balsells *et al.*[1] It is noteworthy that ferric chloride gives a very clean oxidation of

†TLC monitoring; irradiation was stopped as soon as substantial progress of the reaction was noticed. The reaction was quenched by chilling.

benzoin to benzil and may be used as a preparative method for benzil.

All the photolysis products were fully characterised on the basis of elemental analyses and spectral data (PMR) and wherever possible by direct comparison with authentic specimens.

The authors thank the CSIR, New Delhi for the award of senior research fellowship to two of them (S K & V K G).

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Oxidative Cleavage of Some Aldazines

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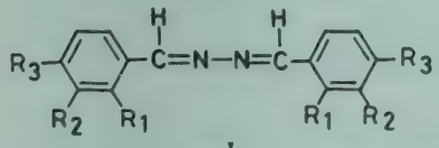
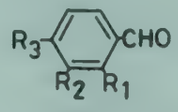
The oxidative cleavage of aldazines (Ia-j) to the corresponding aldehydes with ceric ammonium nitrate is described.

In continuation of our studies on ceric ammonium nitrate (CAN) oxidation[1-4], we report herein the oxidative cleavage of aldazines (Ia-j) with CAN to the corresponding aldehydes. Only a few reports are available in literature[5,6] describing the oxidative cleavage of azines. The aldehydes (II) obtained were characterized viz 2,4-DNP derivatives and direct comparison with those of the authentic samples (Table 1). The mechanism of formation of aldehydes is not clear. The easy conversion of aldehydes to aldazines coupled with their conversion to aldehydes by CAN, makes it an attractive method of protecting an aldehyde group.



I



II

(a) $R_1=R_2=R_3=H$
(b) $R_1=R_2=H$; $R_3=Cl$
(c) $R_1=R_2=H$; $R_3=Br$
(d) $R_1=R_2=H$; $R_3=OCH_3$
(e) $R_1=H$; $R_2=R_3=OCH_3$
(f) $R_1=R_2=H$; $R_3=NO_2$
(g) $R_1=NO_2$; $R_2=R_3=H$
(h) $R_1=R_3=H$; $R_2=NO_2$
(i) $R_1=R_3=H$; $R_2=Cl$
(j) $R_1=Cl$; $R_2=R_3=H$

General Procedure

To a stirred solution of aldazine (0.001 mol) maintained at 80° in acetonitrile (6 ml) was added CAN (0.006 mol) in acetonitrile (6 ml). The reaction mixture was refluxed for 1.5 hr with TLC monitoring. After the reaction was complete, reaction mixture was cooled to room temperature, diluted with water and extraction with ether (2 × 10 ml). The ethereal layer was washed with water, dried (Na_2SO_4) and concentrated. The residual material was reacted with an alcoholic solution of 2,4-dinitrophenyl-hydrazine (in acidic medium). The resulting 2,4-dinitrophenyl hydrazone was coolected by filtration and identified by comparison with authentic sample. The yield and m.ps of the corresponding 2,4-DNP derivatives are listed in Table 1.

Table 1—Oxidative Cleavage of Aldazines with CAN

Aldazine (I)	Aldehyde (II) m.p. (lit.)* (°C)	Yield† (%)
(a)	236-37 (237)	82
(b)	264-65 (265)	79
(c)	264-65 (265)	81
(d)	253-54 (254)	76
(e)	263-64 (264)	75
(f)	319-20 (320)	72
(g)	264-65 (265)	70
(h)	290-92 (292)	80
(i)	247-48 (248)	74
(j)	207-9 (209)	73

*2,4-DNP derivatives.
†Refer to 2,4-DNP derivatives.

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Oxidation of Vasicine by Pyridinium Fluorochromate

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The oxidation of vasicine (I) with pyridinium fluorochromate (PFC) in acidic medium affords vasicinone as the major product and three other oxidation products, structures of which have been assigned on the basis of their spectral data.

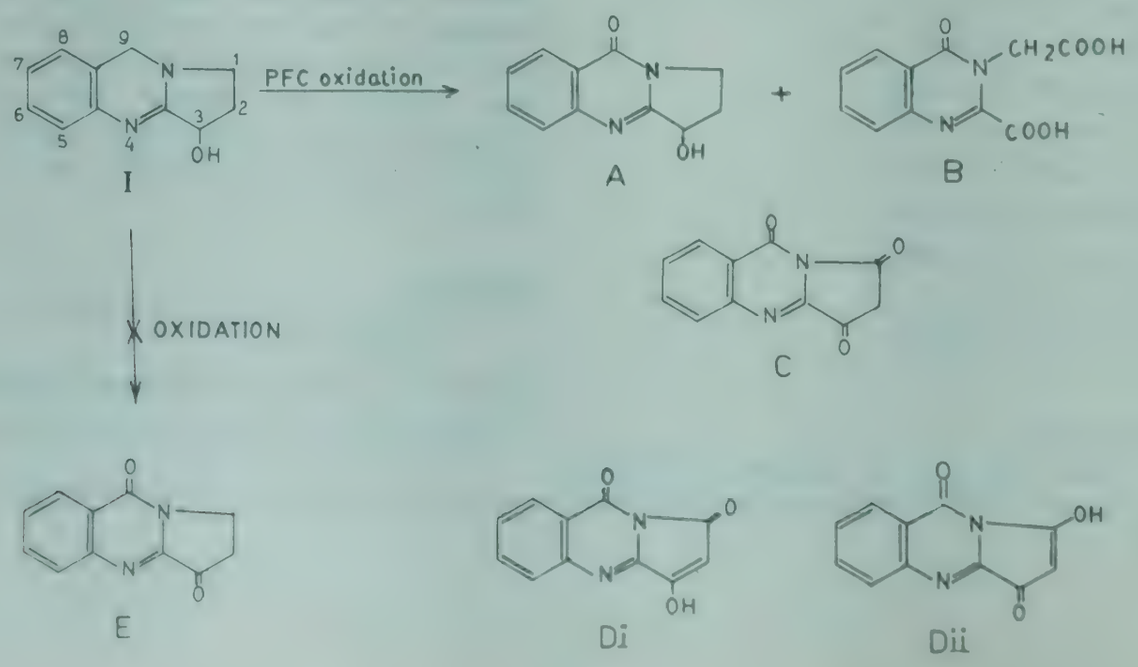
Vasicine (I), an alkaloid isolated earlier from *Adhatoda vasica* Nees, possesses bronchodilatory, oxytocic and abortifacient activities[1]. We report herein the results of oxidation of I with the recently developed oxidant, pyridinium fluorochromate (PFC) in order to identify the sites of oxidation of I and to evaluate activation energy needed for its oxidation under pseudo-first order conditions, i.e. [I] ≫ [oxidant].

Vasicine was isolated from *A. vasica* Nees. PFC was prepared by the procedure given by Bhattacharjee and Choudhuri[2]. All the kinetic measurements were made at 350 nm using SP-500 or SP-700 Pye-Unicam spectrophotometer fitted with thermostated cell compartments. Pseudo-first order rate constants (k_0), bimolecular rate constants (k_2) and slopes for E_a were evaluated by ICL 2960 computer. Details of the kinetic methods are mentioned elsewhere[3,4]. GC/MS was done using a JEOL, JMS-D. 300 column (SE-30, 3 mm × 3 m) with helium as the carrier gas (1.4 kg/cm^2) and column temp = 190-250°C.

The pseudo-first order rate constants for the oxidation of I of varying initial concentrations (1.25 to 10.0×10^{-2} moldm^{-3}) at fixed [oxidant] (1.40×10^{-3} moldm^{-3}) in perchloric acid medium (1.0 moldm^{-3}) increases with increase in [vasicine]. The k_2 values come out to be 1.41×10^{-2} dm^{3}mol^{-1}s^{-1}. A similar behaviour is observed with pyridinium chlorochromate with $k_2 = 1.27 \times 10^{-2}$ dm^{3}mol^{-1}s^{-1}. The E_a value of PFC oxidation is found to be 6.36 kcalmol^{-1}, as compared to 6.72 kcalmol^{-1} for PCC oxidation.

For product analysis vasicine (I, 1.85 g, ≃2.5 mol) was allowed to react with PFC (1 g, 1 mol) in acidic medium. The basic chloroform fraction of the alcoholic extract was subjected to column chromatography over silica gel after removing unreacted I and compound-A was isolated in 45% yield (800 mg). It was found to be TLC single ($CHCl_3$-MeOH, 92:8, R_f 0.65), m.p. 210-11°; UV: 270, 305 and 315 nm; IR: 3161-3121 (OH), 1624 (−C=N−), 1681 (−C−N−) and 1607, 1480 cm^{-1} (aromatic); MS: *m/z* 202 (M^+). The PMR spectrum of compound-A in DMSO-d_6 enhibited two multiplets of two-proton each centred at δ 2.14 and 4.04 attributable to C-2 and C-1 methylenes, a triplet centred at δ 5.04 (1H) and a multiplet centred at 7.6 (3H) assignable to a C-3 methine proton and C-5, -6 and -7 protons respectively. A doublet (J = 8Hz) at δ 8.2 (1H) could be attributed to C_8-H. The proton appearing at δ 6.05 was exchangeable with D_2O.

Acetylation of compound-A yielded a crystalline acetate, m.p. 125-26° which analyzed for $C_{13}H_{12}H_2O_3$ (M^+ 244) and a peak corresponding to the loss of



$COCH_3$ moiety at m/z 201 as the base peak. The PMR spectrum of the acetate in DMSO-d_6 exhibited a signal at δ 6.25 corresponding to a C-3 methine proton. This distinguishable downfield shift of 1.2 ppm of C-3 methine proton in comparison to the parent alkaloid (I) is attributed to acetylation of hydroxyl group at C-3. The spectral data of compound-A and its acetylated product are similar to those of vasicinone and its acetylated product (reported[5] m.p. of vasicinone, 211-12°C). On the basis of these data compound-A is assigned the structure as 1, 2, 3-trihydropyrrolo [2, 1-*b*] quinazolin-3-ol-9[1*H*]-one.

The crude residue (115 mg) obtained after the removal of vasicinone (which formed the major product of oxidation) was dried and methylated with diazomethane[6] and the crude product subjected to GC/MS since the residue showed high retention time and no logical resolution could be achieved. The GC/MS of the product indicated it to be a mixture of at least three compounds. One of the major fractions of GC showed molecular ion peak at m/z 276 (relative abundance 3%) corresponding to compound-B as its methyl ester. The molecular ion peak at m/z 228 of the other fraction could be due to compound DI or DII (as its methyl ether). Its mass spectrum showed a prominent peak at m/z 213 corresponding to loss of $-OCH_3$. The third fraction with high retention time showed the molecular ion peak at m/z 214 which could be assigned to compound-C (a triketone).

The formation of vasicinone (A) as the major oxidation product with 3-OH remaining unaffected is difficult to explain. We believe that OH in vasicine is not oxidized since it is in between two nitrogen atoms which are equidistant from oxygen centre forming N $-$N$-$O triangle[1]. Hence position-9 of vasicine (I) can be considered as most susceptible position for oxidation.

One of the authors RKD is thankful to the IIT, New Delhi for the award of a senior research fellowship. Vasicine was a gift sample from Dr S C Taneja and Dr Surinder Koul of RRL, Jammu-Tawi.

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18-Deoxysagittariol from *Sagittaria sagittifolia*† Linn.

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On the basis of spectroscopic data, including ^{13}C NMR, the new diterpene isolated from *Sagittaria sagittifolia* Linn. has been shown to be an A/B *cis* clerodanic diterpene, and is assigned the structure as 18-deoxysagittariol (1).

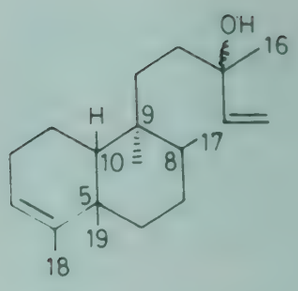
Sagittaria sagittifolia Linn. (Alismaceae) is an aquatic herb found locally in the banks of rivers and ponds. Sagittariol[1,2], a compound recently isolated from this plant, has been shown[1,2] to be a clerodane diterpene instead of belonging to labdane series. From the hexane soluble part another viscous oily compound, 18-deoxysagittariol (1) has been isolated through column chromatography. This note deals with the structure elucidation of **1**.

Compound (1), $C_{20}H_{34}O$ (M^+ 290), $[\alpha]_D+29°$, exhibits in its IR spectrum (neat) peaks at 3367 (OH), 1635, 994, 923 ($CH=CH_2$), 1669, 879, 833 cm^{-1} ($C=CH$). It had no UV absorption above 217 nm, was bicyclic in nature, and its PMR spectrum displayed signals at δ 5.25 (1H, $W_{1/2}=8$Hz, H-3), an *ABX* pattern for three vinylic protons at 5.87 (H_X), 5.13 (H_B) and 4.98 (H_A) ($J_{AX}=17$; $J_{BX}=10$ and $J_{AB}=1.5$Hz) and other signals at 0.80, 1.02, 1.23 (each *s*, 3H each), 0.76 (*d*, $J=6$Hz) and 1.67 (*bs*, 3H, vinylic methyl). Compound (1) was assigned a clerodane skeleton with *cis*-fused rings A and B on the basis of a low field resonance of a bridge head methyl carbon (33.05 ppm)[2] as in the case of sagittariol (2).

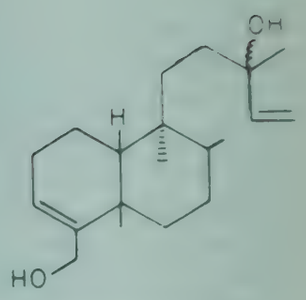
Compound (1) was acetylated (Py/Ac_2O, N_2 atm). In the PMR spectrum of the acetate signal for C-13 methyl protons shifted upfield from δ 1.23 to 1.53. In the presence of trichloroacetyl isocyanate, the methyl signal shifted to δ 1.67. These observations confirmed the presence of $-C(OH)-CH_3$ grouping in the molecule.

The mass spectrum of **1** indicated the base peak at *m/z* 191 (M-side chain); other prominent peaks were at *m/z* 272 and 257 arising by the successive loss of H_2O and a methyl group from M^+.

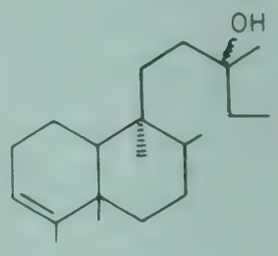
On hydrogenation under high pressure in the presence of PtO_2 as catalyst, both **1** and **2** gave a common product 18-deoxydihydrosagittariol (**3**),



(1)



Sagittariol (2)



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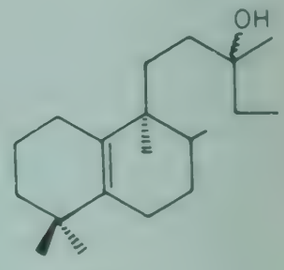

(4)

which on treatment with HCl/AcOH for 48 hr gave an isomerised product (**4**)[3] as a viscous material purified by preparative TLC. The formation of **4** was confirmed by the absence of vinylic methyl and vinylic proton signals in its PMR spectrum; other signals for methyl protons appeared at δ 0.74 (*s*), 0.80 (*d*, $J=6$Hz), 0.83 (*t*), 0.96 (*s*, 6-H) and 1.25 (*s*). The foregoing evidences confirm structure (**1**) for 18-deoxysagittariol.

UV spectra was taken in MeOH, ^{13}C, ^1H, NMR spectra were taken in R-32 and 400 MHz spectrophotometer with TMS as internal standard and $CDCl_3$ as a solvent, unless otherwise indicated.

Isolation of **1**

The dry powdered plant (8 kg) was extracted thoroughly with ethanol, the ethanolic extract concentrated, partitioned with hexane, $CHCl_3$ and *n*-BuOH. The hexane soluble fraction (100 g) was chromatographed over neutral alumina. On elution with hexane-benzene (3:1) crude **1** (2 g) was obtained, which was further purified by column chromatography and finally by preparative TLC; ^{13}C NMR: **1**: δ 17.43 (1), 24.09 (2), 123.19 (3), 144.96 (4), 36.18 (5), 36.89 (6), 28.8 (7), 37.33 (8), 39.88 (9), 44.62 (10), 31.62 (11), 35.24 (12), 73.46 (13), 145.24 (14), 111.75 (15), 27.67 (16), 15.92 (17), 17.71 (18), 33.05 (19), 17.43 (20).

18-Deoxydihydrosagittariol (**3**)

1 (20 mg) on hydrogenation over Pt_2O (2 mg) for 3 hr at room temperature and pressure afforded **3** as a

†CDRI Communication No. 3766.

viscous liquid; PMR: δ 0.75 (*d*, J = 6Hz, 8-Me), 0.85 (9-Me), 0.96 (*t*, 15-Me), 1.1 (5-Me), 1.2 (13-Me), 1.64 (*bs*, 4-Me); other proton signals appeared in the region 2.0 and 0.9. The 400MHz PMR spectrum of **3** obtained by the reduction of sagittariol (**2**) displayed signals at δ 0.77 (*d*, J = 6Hz, 8-Me), 0.83 (9-Me), 0.91 (*t*, 15-Me), 1.03 (5-Me), 1.17 (13-Me), 1.5 (1H, *m*, H-8), 1.68 (*bs*, 4-Me); MS: *m/z* 292 (37.0%, M^+), 275, 260, 191, 123, 121, 109, 107, 95 (base peak).

Isomerisation of **3**

Dihydrodeoxysagittariol (**3**, 50 mg) was dissolved in a mixture containing 0.5 ml conc. HCl and 0.3 ml acetic acid and the mixture kept for 48 hr. Work-up followed by extraction with ether afforded crude **4**, which was purified by preparative TLC (hexane) to furnish **4** as a viscous liquid.

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Rare Occurrence of Δ^7-Sterols in *Celosia cristata* Linn.

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The fraction of sterols isolated from the pet. ether extract of the herb *Celosia cristata* Linn. consists exclusively of Δ^7-sterols, rarely found in seed bearing plants. Its GLC analysis shows the presence of 24-ethyl-22-dehydrolathosterol (24-ethyl-5α-cholesta-7,*trans*-22-dien-3β-ol; 69.6%) and 24-ethyllathosterol (17.5%) in major amounts together with 24-methyl-22-dehydrolathosterol (3.8%), 24-methyllathosterol (3.9%), 24-methylenelathosterol (1.9%) and 24-ethylidenelathosterol (Δ^7-avensaterol; 3.3%).

Celosia cristata Linn. (Amaranthaceae), commonly known as 'La Murghka' in Hindi is a pot herb and grown in gardens for ornamental purposes. Since this herb is used for various medicinal purposes[1] and no work seems to have been carried out so far on its chemical constituents, the pet. ether extract of this herb has been studied in an attempt to characterise its steroidal constituents and the results are reported in this note.

The air-dried herb, collected from the surroundings of Aligarh, was ground and extracted three times with pet. ether (b.p. 60-80°) under reflux for 18 hr. Removal of solvent under reduced pressure yielded a greenish dry mass (2% of the herb) which after purification was subjected to column chromatographic separation over silica gel (~20 fold excess).

The sterol fraction (% of the crude) was obtained from benzene eluates and purified by trituration from chloroform-methanol, m.p. 150°, gave +ve L.B. test and exhibited prominent IR bands at 3420 and 1045 cm^{-1} (OH). Its acetyl derivative exhibited IR bands at 1725 and 1242 cm^{-1} and gave three spots on TLC plate coated with silica gel-20% $AgNO_3$, when developed five times with CH_2Cl_2-CCl_4 (1:4) as irrigant.

The qualitative and quantitative composition of sterol fraction was determined by GLC as 24-methyl-22-dehydrolathosterol (I, 24-methyllathosterol (II), 24-methylenelathosterol (III), 24-ethyl-22-dehydrolathosterol (IV), 24-ethyllathosterol (V) and 24-ethylidenelathosterol (VI) and identified as acetates on the basis of RRT (Table 1).

The acetyl derivatives of the sterols IV, V and VI were separated by reverse phase HPLC and characterised as 24-ethyl-22-dehydrolathosterol (α-spinasterol), 24-ethyllathosterol and 24-ethylidenelathosterol on the basis of their mass spectra exhibiting a molecular ion (M^+) at *m/z* 454 (relative intensity 20%) accompanied by the fragmentation ions at *m/z* [7%, $M-CH_3$)], 411 [17%, (M − isopropyl gp), characteristic for Δ^{22}-sterols], 379 [6%, $M-(AcOH+CH_3)$], 351 [23%, M − (AcOH + isopropyl gp)], 315 [22%, (M − side chain)], 313 [100%, M − (side chain + 2H)], 273 [11%, M − (side chain + 42)], 255 [75%, M − (side chain + AcOH)], 213 [31%, M − (side chain + 42 + AcOH)][2-3]; a molecular ion (M^+) at *m/z* 456 (relative intensity 51%) accompanied by the fragementation ions at *m/z* 441 [14%, $(M-CH_3)$], 381 [11%, $M-AcOH+CH_3$)], 315 [5%, M − (side chain + 2H)], 273 [16%, M − (side chain + 42)], 255 [100%, M − (side chain + AcOH)], 213 [53%, M − (side chain + 42 + AcOH)] and a molecular ion (M^+) at *m/z* 454 (very small peak) accompanied by the fragmentation ions at *m/z* 439 [2%, $(M-CH_3)$], 379 [3%, $M-(AcOH+CH_3)$], 356 (M − a part of side chain C_7H_{14}, 98)], 341 [5%, M − (a part of side chain $+CH_3$)], 313 [100%, M − (side chain + 2H)], 296 [7%, $M-(C\text{-}H_{14}+AcOH)$], 253 [14%, M − (side chain + 2H + AcOH)], 213 [20%, M − side chain + 42 + AcOH)] respectively.

The sterol fraction of the herb *C. cristata* was thus demonstrated to contain exclusively Δ^7-sterols. The vast majority of seed bearing plants (spermatophyta)

Table 1—Various Δ^7-Sterols Isolated from the Pet. Ether Extract of *C. cristata* Linn.

Sl. No	Sterol	Presence of double bond	Other structural characteristics	*RRT	Percentage compositin
1	24-Methyl-22-dehydrolathosterol	7, 22	$24R-CH_3$	1.35	3.8
2	24-Methyllathosterol	7	$24R-CH_3$	1.53	3.9
3	24-Methylenelathosterol	7, 24(28)	$24R-CH_3$	1.62	1.9
4	24-Ethyl-22-dehydrolathosterol	7, 22	$24R-C_2H_5$	1.68	69.6
5	24-Ethyllathosterol	7	$24R-C_2H_5$	1.92	17.5
6	24-Ethylidenelathosterol	7, 24(28)	$24R-C_2H_4$	2.13	3.3

*The retention time of cholesteryl acetate (5.25 min) was taken as one.

contain 24-alkyl-Δ^5-sterols as the principal sterol components and the predominance of Δ^7-sterols appears to be restricted to a few plant families such as Theaceae and Cucurbitaceae[2-4]. It is of interest from the view point of chemical taxonomy that genus *Celosia* of family Amaranthaceae falls into the rare class of seed bearing plants which contains exclusively Δ^7-sterols,

The acetylation was accomplished with acetic anhydride and pyridine keeping overnight at room temperature and then heating for 6 hr.

GLC of the acetylated sterol fraction was performed on a Shimadzu GC-4CM gas chromatograph equipped with a flame ionization detector[5]. The chromatograph was fitted with an OV-17 SCOT glass capillary column (30 m × 0.3 mm i.d.). The column was operated at 260° with nitrogen at 60 ml/min as carrier gas at the split ratio 100: 1. Injection temperature was 290°. Preparative HPLC was performed on an ERC 8710 HPLC system [Erma optical works, Tokyo] equipped with an ERC 7520 RI detector. The system was operated on a partisil 5 ODS-2 (Whatman 25 cm × 10 mm i.d) reverse phase column with a mobile phase consisting of methanol-water (98 : 2). The relative retention times (RRT's) of the steryl acetates on GLC and HPLC were relative to cholesteryl acetate.

The mass spectra were measured on a Hitachi RMU-7M mass spectrometer at 70 eV introducing the samples by means of a probe injection. IR spectra were taken in nujol mull.

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Synthesis of 4-(2′-Methoxy-5′-methylphenyl)-6-methylheptan-2-one, a Seco-sesquiterpene Structural Analogue of Sesquichamaenol & Himasecolone†

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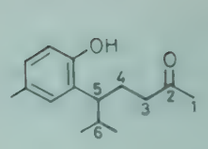
4-(2′-Methoxy-5′-methylphenyl)-6-methylheptan-2-one (V), a seco-sesquiterpenoid structurally analogous to sesquichamaenol (I) and himasecolone (II), has been synthesized in one step by the conjugate addition of 2-methoxy-5-methylphenylmagnesium bromide to 6-methylhept-3-en-2-one (X). The possible biogenetic origin of V has been indicated.

Sesquichamaenol[1] [5-(2′-hydroxy-5′-methylphenyl)-6-methylheptan-2-one] (I) and himasecolone[2] [6-(2′-hydroxy-5′-methylphenyl)-6-methylheptan-2-one] (II) are naturally occurring 5- and 6-aryl (2-*p*-cresyl) derivatives of 6-methylheptan-2-one and their syntheses have been reported[1,3-6]. In particular, II[4,5] was synthesised in our laboratory two years before it was isolated from a natural source[2]. The biogenetic origin of the phenolic ketones (I and II) is tentatively traced to δ-cadinene (III) and β-himachalene (IV) from which I and II are hypothesized to arise by oxidative cleavage, accompanied by aromatization of the B-ring. Following this line of our earlier speculation[4], we undertook the synthesis of a structurally analogous sesquiterpenoid, 4-(2′-methoxy-5′-methylphenyl)-6-methylheptan-2-one (V) which may be biogenetically related likewise to the hydrindane (VI), the carbon skeleton of which is revealed in the natural products, mutisianthol[7] (VII) and jungianol[8] (VIII).

The synthesis of the seco-sesquiterpene (V) was accomplished in one step by the cuprous iodide catalysed 1,4-addition[9] of the Grignard reagent prepared from 2-methoxy-5-methylbromobenzene[10] (IX) to 6-methylhept-3-en-2-one[11] (X). Attempted demethylation of the resulting keto aryl methyl ether using a few conventional demethylating agents such as HBr-AcOH, BBr_3, NaSEt, pyridine hydrochloride[12] failed to produce the corresponding free phenol.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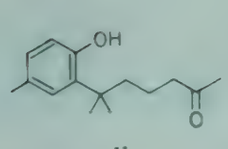
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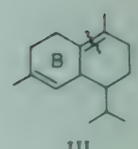
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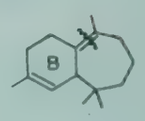
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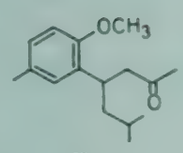
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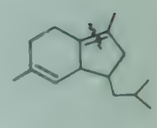
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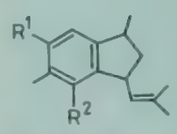
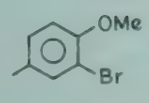

VII : $R^1 = OH$; $R^2 = H$
VII : $R^1 = H$; $R^2 = OH$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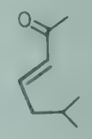
X

4′-(2′-*Methoxy-5′-methylphenyl*)-6-*methylheptan-2-one* (*V*)

To the Grignard reagent, prepared from IX (4 g) in dry ether (20 ml) and magnesium turnings (0.5 g) covered by dry ether (30 ml) by stirring overnight at room temperature, cuprous iodide (3.8 g) was added and the stirring continued for 1 hr. To the reaction mixture, X (2.3 g) in dry ether (10 ml) was added dropwise with stirring. The stirring was continued overnight and then the reaction mixture was heated to reflux for 4 hr. Decomposition with saturated aq. NH_4Cl (100 ml), extraction with ether and column chromatographic purification (silica gel-hexane) of the product gave V; IR (neat): 1700, 1505, 1250, 1040 and 800 cm^{-1}; PMR (100 MHz, CCl_4): δ 0.76-0.94 (6H, merged, CH_3CHCH_3), 1.12-1.7 [2H, merged, $CHCH_2CH(CH_3)_2$], 1.9 (3H, *s*, $COCH_3$), 2.22 (4H, *bs*, $Ar-CH_3$ & $Ar-CH$), 2.54 (2H, *d*, $J = 7$ Hz, CH_2CO), 3.76 (3H, *s*, OCH_3) and 6.6-6.9 (3H, *m*, Ar-*H*) (Found: C, 77.3; H, 9.9. $C_{16}H_{24}O_2$ requires C, 77.4; H, 9.7%).

We are indebted to the UGC, New Delhi for financial assistance.

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Synthesis of 8-(3,3-Dimethylallyl)-5,7-dimethoxyflavanone

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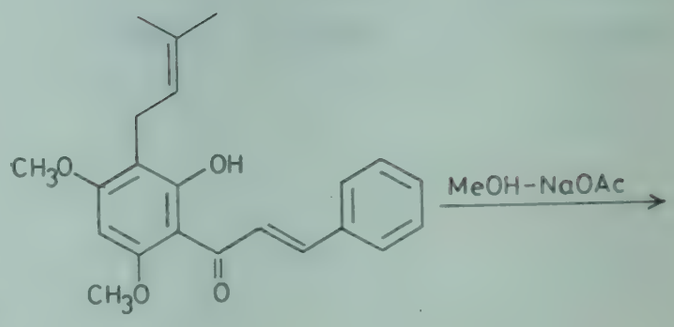
The title compound (2) has been synthesised by cyclisation of 2′-hydroxy-4′,6′-dimethoxy-3′-C-prenylchalcone (1) with methanolic sodium acetate.

From the seeds of *Lonchocarpus costaricensis*, Waterman and Mahmoud[1] isolated very recently four new flavonoids, one of which was assigned the structure 8-(3,3-dimethylallyl)-5,7-dimethoxyflavanone (2) on the basis of its PMR, ^{13}C-NMR and EIMS data. We had a sample of 4,6-dihydroxy-2-methoxy-5-C-prenylacetophenone[2], which on partial methylation of hydroxyl group in position-4 and subsequent condensation with benzaldehyde yielded 2′-hydroxy-4′,6′-dimethoxy-3′-C-prenylchalcone[3] (1). In the present study cyclisation of 1 with methanolic sodium acetate has afforded the flavanone (2) identical with the natural sample in m.p., UV, IR and PMR data.



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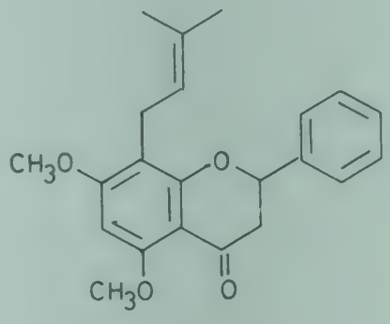

(2)

8-(3,3-*Dimethylallyl*)-5,7-*dimethoxyflavanone* (2)

A solution of 2′-hydroxy-4′,6′-dimethoxy-3′-C-prenylchalcone[3] (1, 0.2 g) in methanol (20 ml) was warmed at 40-45° with anhyd. sodium acetate (0.5 g) for 50 hr. The mixture was poured into cold water and the solid collected. It crystallised from benzene-petroleum ether mixture to give 2 as colourless needles (0.12 g), m.p. 99-100° (lit.[1] 98°); gave negative ferric reaction and was identical with the natural sample in UV, IR and PMR data.

The authors express their gratitude to CSIR, New Delhi for the grant of SRF to one of them (O D T).

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Aromatic Benzhydrylation: Part VI—Synthesis of Triarylmethane Types of Acetophenones, Chalkones & 2-Methylchromones

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Resacetophenone (**1**) on treatment with diphenylcarbinol in the presence of $BF_3.Et_2O$ affords a mixture of 3-diphenylmethyl-(**3a**; 21.4%), 5-diphenylmethyl-(**4a**; 39.3%), and 3,5-bisdiphenylmethyl-(**2a**; 14.3%) derivatives which on heating with sodium acetate and acetic anhydride under Perkin's conditions give the corresponding 7-acetoxy-3-acetyl-2-methylchromones (**6a**, **6c** and **6e**). Alkaline hydrolysis of **6a-c** yields the corresponding 7-hydroxychromone (**6b**, **6d** and **6f**). Triarylmethane types of chalkones (**5a**, **5b** and **5c**) have been prepared from the corresponding acetophenones (**2c**, **3c** and **4c**). All the new compounds have been characterized by their UV, IR and PMR data.

Recently in this laboratory, phloroacetophenone[1], its 2-methyl ether[2] and gallacetophenone[1] were subjected to aromatic benzhydrylation with diphenylcarbinol in the presence of $BF_3.Et_2O$ giving a mixture of benzhydrylated compounds in each case which were converted into chalkones, chromones and flavones. As an extension of this work, aromatic benzhydrylation of resacetophenone (**1**) has now been studied in detail and the resulting triarylmethane types of acetophenones converted into the corresponding chalkones and chromones as analogues of biologically active natural compound melanervin[3,4].

Resacetophenone (**1**)[5] on reaction with diphenylcarbinol in dioxane in the presence of $BF_3.Et_2O$ gave a mixture of three products which were separated by column chromatography. The products were identified as 2,4-dihydroxy-3,5-bisdiphenylmethyl-(**2a**), 2,4-dihydroxy-3-diphenylmethyl-(**3a**) and 2,4-dihydroxy-5-diphenylmethyl-acetophenones (**4a**) on the basis of methylation and PMR studies.

The partial methyl ethers (**2c**, **3c** and **4c**) of the above products were separately condensed with benzaldehyde in ethanolic KOH to give the corresponding benzhydrylated chalcones (**5a**, **5b** and **5c**) which were characterised by their UV and PMR spectra.

The benzhydrylated acetophenones (**2a**, **3a** and **4a**) were also reacted with sodium acetate and acetic anhydride under Perkin's conditions to give the corresponding 7-acetoxy-3-acetyl-2-methylchromones (**6a**, **6c** and **6e**) which on deacetylation with boiling aq. Na_2CO_3 afforded the corresponding 7-hydroxy-2-methylchromones (**6b**, **6d** and **6f**). The products in each case were also characterised by their spectral data.

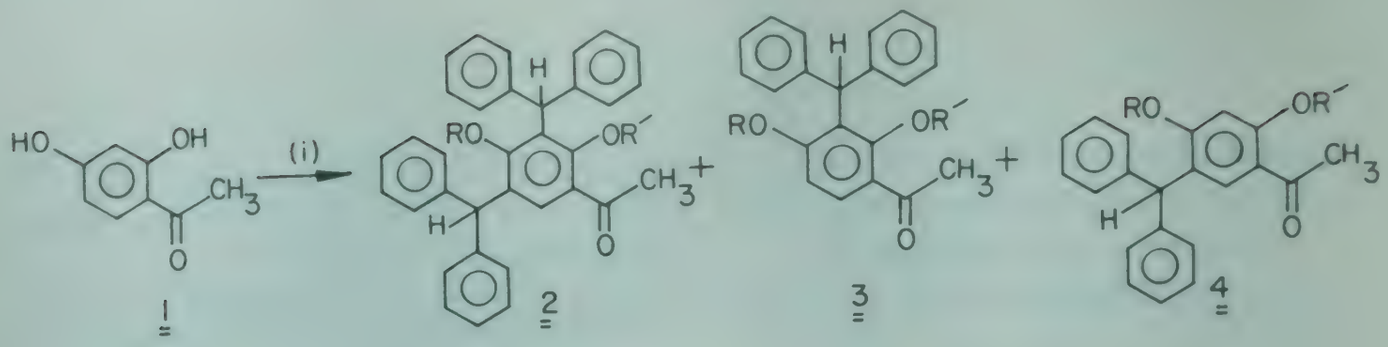
Since in the above acetophenones (**2b**, **c**, **3b**, **c** and **4b**, **c**) and chromones (**6a**, **6c** and **6e**), the position of diphenylmethyl group could be unambiguously settled by PMR data, the interaction between methoxy/acetoxy group and diphenylmethyl group was also studied. Table 1 shows that in acetophenones, 3-diphenylmethyl group shields C_2-methoxyl to the maximum extent whereas 5-diphenylmethyl group has a minor effect. On the other hand, if both 3- and 5-positions are occupied by diphenylmethyl group, both C_2- and C_4-methoxyl are shielded. Similarly, Table 2 shows that 7-acetoxyl gets shielded in chromones if both 6- and 8-positions are blocked. However, when only one diphenylmethyl group is present, no effect is felt on 7-acetoxyl. The methine proton is more downfield in 8-position than in 6-position. Further 7-acetoxy shields this methine signal in all the cases.

Table 1—Comparison of Methoxyl Signals in PMR Spectra of Benzhydrylated Acetophenones

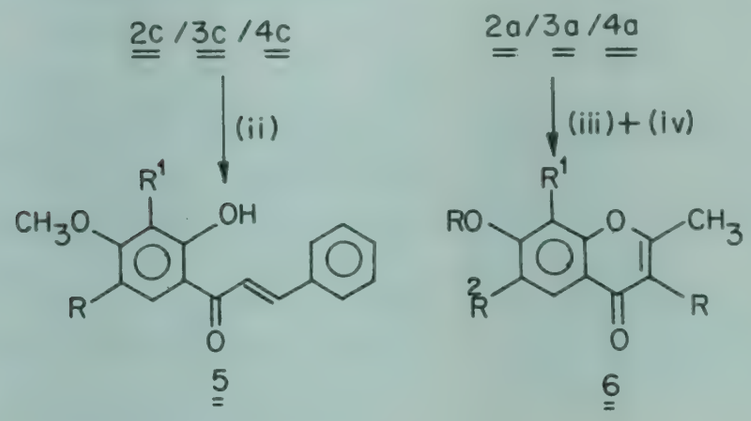
Compd	δ OCH_3 at	
	C-2	C-4
2b	2.92	3.08
2c	—	3.13
3b	3.30	3.85
3c	—	3.64
4b	3.75	3.90
4c	—	3.69

Table 2—Comparison of Acetoxyl and Benzhydryl Methine Signals in Chromones

Compd	δ $OCOCH_3$	δ $CHPh_2$ at	
		C-6	C-8
6a	1.90	5.50	5.68
6c	2.29	—	6.11
6e	2.30	5.53	—
6b	—	5.75	6.0
6d	—	—	6.30
6f	—	5.8	



For 2-4 : a, R = R′ = H ; b, R = R′ = CH_3; c, R = CH_3, R′ = H



a, R = R¹ = —CH(Ph)Ph

b, R = H; R¹ = —CH(Ph)Ph

c, R = —CH(Ph)Ph ; R¹ = H

a, R = —$COCH_3$, R¹ = R² = —CH(Ph)Ph

b, R = H, R¹ = R² = —CH(Ph)Ph

c, R = —$COCH_3$, R¹ = —CH(Ph)Ph, R² = H

d, R = H, R¹ = —CH(Ph)Ph, R² = H

e, R = —$COCH_3$ R¹ = H , R² = —CH(Ph)Ph

f, R = H, R¹ = H, R² = —CH(Ph)Ph

Reagents used

(i) $(Ph)_2CHOH$, BF_3 —Et_2O, dioxane

(ii) PhCHO, CH_3OH – KOH

(iii) Ac_2O, NaOAc

(iv) 10 % aq. Na_2CO_3

Unless stated otherwise, all m.ps are uncorrected; petrol used had boiling range 60-80°; silica gel was used for column chromatography as well as TLC; R_f values refer to TLC in either (A) benzene, or (B) benzene – EtOAc (9:1); UV spectra were recorded in methanol on a Perkin-Elmer 554 spectrophotometer (λ_{max} in nm and log ε values in parenthesis); IR spectra were run in KBr on a Perkin-Elmer 621 IR spectrophotometer (ν_{max} in cm^{-1}); 90 MHz PMR spectra were recorded on a Perkin-Elmer R-32 spectrometer using TMS as internal standard (chemical shifts in δ, ppm and J values in Hz).

Reaction of 2,4-*dihydroxyacetophenone* (**1**) *with diphenylcarbinol*

To a solution of **1** (1.40 g, 9.6 mmol) in dry dioxane (150 ml) was added a solution of diphenylcarbinol (1.80 g, 9.6 mmol) in dioxane (20 ml) followed by $BF_3.Et_2O$ (15 ml). The resulting solution was stirred at room temperature for 4 hr, diluted with moist ether, and the ethereal layer washed with water, dried and evaporated. The residue on column chromatography and successive elution with (i) petrol, (ii) petrol-benzene (19:1), (iii) petrol-benzene (9:1), and (iv) petrol-benzene (2:3) gave four fractions (A-D).

Fraction A—It crystallised from petrol to give **2a** as colourless needles (200 mg), m.p. 144-45°; gave greenish-violet ferric reaction; R_f 0.74 (solvent-A) (Found: C, 84.6; H, 5.4. $C_{34}H_{28}O_3$ requires C, 84.3; H, 5.8%); UV: 278 (3.65), 202 (4.61); IR: 3450, 3045, 3020, 1625, 1590; PMR: 2.20 (*s*, 3H, $-COCH_3$), 5.63 and 6.23 [2*s*, 1H each, $2\times -CH(Ph)_2$], 7.18 (b*m*, 2OH, $4\times C_6H_5$), 7.53 (*s*, 1H, C_6-H) and 13.40 (*s*, 1H, chelated $-OH$).

An acetone solution of **2a** (0.1 mmol) was refluxed with Me_2SO_4 (0.02 ml, 0.2 mmol) and dry K_2CO_3 (55 mg, 0.4 mmol) for 6 hr and the completely methylated product (**2b**) worked up as usual. It crystallised from petrol as colourless plates (45 mg), m.p. 95-96°; gave no colour with $FeCl_3$; R_f 0.43 (solvent-A) (Found: C, 84.0; H, 6.5. $C_{36}H_{32}O_3$ requires C, 84.3; H, 6.3%); PMR: 2.49 (*s*, 3H, $-COCH_3$), 2.92 & 3.08 (2*s*, 3H each, $2\times -OCH_3$), 5.89 and 6.10 [2*s*, 1H each, $2\times -CH(Ph)_2$], 7.15 (*bm*, 20H, $4\times C_6H_5$), and 7.56 (*s*, 1H, C_6-H).

A solution of **2a** (0.1 mmol) was refluxed with Me_2SO_4 (0.01 ml, 0.1 mmol) and anhyd. K_2CO_3 for 15 min and the partial methyl ether (**2c**) worked up as usual. It crystallised from petrol-benzene as colourless needles (40 mg), m.p. 152-53°; gave brown ferric reaction; R_f 0.56 (solvent-A) (Found: C, 83.9; H, 6.2. $C_{35}H_{30}O_3$ requires C, 83.9; H, 6.1%); PMR: 2.29 (*s*, 3H, $-COCH_3$), 3.13 (*s*, 3H, $-OCH_3$), 5.85 and 6.05 [2*s*, 1H each, $2\times -CH(Ph)_2$], 7.15 (b*m*, 2OH, $4\times C_6H_5$), 7.50 (*s*, 1H, C_6-H) and 12.69 (*s*, 1H, chelated OH).

Fraction B—It crystallised from petrol-benzene to give **3a** as colourless needles (300 mg), m.p. 203-4°; gave greenish violet ferric reaction; R_f 0.51 (solvent-A) (Found: C, 79.1; H, 5.4. $C_{21}H_{18}O_3$ requires C, 79.2; H, 5.7%); UV: 280 (4.24), 210 (4.58); IR: 3310 (br), 1625, 1595; PMR: 2.64 (*s*, 3H, $-COCH_3$), 6.18 [*s*, 1H, $-CH(Ph)_2$], 6.43 (*d*, $J=10$ Hz, 1H, C_5H), 7.30 (b*m*, 10H, $2\times C_6H_5$) and 7.64 (*d*, $J=10$ Hz, 1H, C_6-H).

The fully methylated derivative (**3b**) crystallised from petrol as colourless plates (80 mg), m.p. 105-6°; R_f 0.15 (solvent-A) (Found: C, 79.6; H, 6.6. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%); PMR: 2.60 (*s*, 3H, $-COCH_3$), 3.30 and 3.55 (2*s*, 3H each, $2\times -OCH_3$), 6.15 [*s*, 1H, $-CH(Ph)_2$], 6.70 (d, $J=10$ Hz, 1H, C_5-H), 7.30 (b*m*, 10H, $2\times C_6H_5$) and 7.65 (*d*, $J=10$ Hz, 1H, C_6-H).

The partial methyl ether (**3c**) crystallised from benzene-petrol as colourless needles (30 mg), m.p. 161-62°; gave brown ferric reaction; R_f 0.44 (solvent-A) (Found: C, 79.9; H, 6.1. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%); PMR: 2.52 (*s*, 3H, $-COCH_3$), 3.64 (*s*, 3H, $-OCH_3$), 6.14 [*s*, 1H, $-CH(Ph)_2$], 6.42 (*d*, $J=10$ Hz, 1H, C_5-H), 7.20 (*bm*, 10H, $2\times C_6H_5$), 7.64 (*d*, $J=10$ Hz, 1H, C_6-H) and 12.97 (*s*, 1H, chelated $-OH$).

Fraction C—It crystallised from benzene to give **4a** as cream coloured needles (550 mg), m.p. 179-80°; gave greenish violet ferric reaction; R_f 0.17 (solvent-A) (Found: C, 79.6; H, 5.5. $C_{21}H_{18}O_3$ requires C, 79.2; H, 5.7%); UV: 276 (4.21), 202 (4.67); IR: 3210 (br), 3020, 1625, 1600; PMR: 2.22 (*s*, 3H, $-COCH_3$), 5.59 [*s*, 1H, $-CH(Ph)_2$], 6.20 (*s*, 1H, C_3-H), 7.11 (*bm*, 10H, $2\times C_6H_5$), 7.65 (*s*, 1H, C_6-H) and 12.80 (*s*, 1H, chelated $-OH$).

The fully methylated derivative (**4b**) crystallised from petrol as colourless plates (80 mg), m.p. 140-41°, R_f 0.38 (solvent-A) (Found: C, 79.3; H, 6.7. $C_{23}H_{22}O_3$ requires C, 79.7; H, 6.4%); PMR: 2.49 (*s*, 3H, $-COCH_3$), 3.75 and 3.90 (2*s*, 3H each, $2\times -OCH_3$), 5.75 [*s*, 1H, $-CH(Ph)_2$], 6.40 (*s*, 1H, C_3-H), 7.15 (*bm*, 10H, $2\times -C_6H_5$) and 7.40 (*s*, 1H, C_6-H).

The partial methyl ether (**4c**) crystallised from benzene-petrol as colourless plates (30 mg), m.p. 145-46°; R_f 0.44 (solvent-A) (Found: C, 79.1; H, 5.9. $C_{22}H_{20}O_3$ requires C, 79.5; H, 6.1%); PMR: 2.22 (*s*, 3H, $-COCH_3$), 3.69 (*s*, 3H, $-OCH_3$), 5.69 [*s*, 1H, $CH(Ph)_2$], 6.33 (*s*, 1H, C_3-H), 7.10 (*bm*, 10H, $2\times C_6H_5$), 7.0 (*s*, 1H, C_6-H) and 12.80 (*s*, 1H, chelated OH).

Chalkone condensation of partial methyl ethers (**2c**, **3c** *and* **4c**)

To a solution of the substrate in methanol (4 ml) and KOH (28 mg, 0.5 mmol) was added freshly distilled benzaldehyde (0.01 ml, 0.1 mmol) with constant stirring. The resulting solution was kept overnight, poured into ice-cold water and acidified with dil. HCl. The solid thus separated was collected and crystallized from MeOH to give the chalkone.

3′,5′-Bisdiphenylmethyl-2′-hydroxy-4′-methoxychalkone (**5a**): Pale yellow plates (40 mg), m.p. 177-78°; gave light brown ferric reaction; R_f 0.64 (solvent-A) (Found: C, 85.6; H, 5.4. $C_{42}H_{34}O_3$ requires C, 86.0; H, 5.8%); UV: 326 (3.93), 286 (4.58) and 206 (4.58); IR: 3015, 1620, 1600 and 1565; PMR: 3.2 (*s*, 3H, $-OCH_3$), 5.78 and 5.90 [2*s*, 1H each, $2\times CH(Ph)_2$], 7.05 (*bm*, 26H, $5\times C_6H_5$ and $C_\alpha-H$), 7.30 (*d*, $J=18$ Hz, 1H, $C_\beta-H$), 7.40 (*s*, 1H, $C_{6'}-H$) and 12.60 (*s*, 1H, chelated $-OH$).

3′-Diphenylmethyl-2′-hydroxy-4′-methoxychalkone (**5b**): Pale yellow needles (25 mg), m.p. 119-20°; gave a light brown colour with $FeCl_3$; R_f 0.64 (solvent-A)

(Found: C, 82.9; H, 5.8. $C_{29}H_{24}O_3$ requires C, 82.9; H, 5.8%); UV: 320 (4.08), 286 (4.11), 208 (4.63); IR: 3015, 1620, 1600, and 1565; PMR: 3.65 (*s*, 3H, $-OCH_3$), 6.10 [*s*, 1H, $-CH(Ph)_2$], 6.39 (*d*, $J=10$ Hz, 1H, $C_{5'}-H$), 7.10 (*bm*, 15H, $3\times -C_6H_5$), 7.32 (*d*, $J=18$ Hz, 1H, $C_\alpha-H$), 7.42 (*d*, $J=18$ Hz, 1H, $C_\beta-H$), 7.72 (*d*, $J=10$ Hz, 1H, $C_{6'}-H$) and 13.20 (*s*, 1H, chelated $-OH$).

5'-Diphenylmethyl-2'-hydroxy-4'-methoxychalkone (**5c**): Pale yellow plates (25 mg), m.p. 95-96°, gave light brown ferric reaction; R_f 0.64 (solvent-A) (Found: C, 82.4; H, 5.8. $C_{29}H_{24}O_3$ requires C, 82.8; H, 5.7%); UV: 314 (4.24), 270 (4.10) and 210 (4.72); IR: 3055, 3020, 1620, 1610 and 1595; PMR: 3.70 (*s*, 3H, $-OCH_3$), 5.70 [*s*, 1H, $-CH(Ph)_2$], 6.35 (*s*, 1H, $C_{3'}-H$), 7.12 (*bm*, 15H, $3\times C_6H_5$), 7.28 (*d*, $J=18$ Hz, 1H, $C_\alpha-H$), 7.42 (*d*, $J=18$ Hz, 1H, $C_\beta-H$), 7.60 (*s*, 1H, $C_{6'}-H$) and 13.28 (*s*, 1H, chelated $-OH$).

Perkin reaction of **2a**, **3a** *and* **4a**

A mixture of the ketone (240 mg), fused NaOAc (500 mg) and Ac_2O (5 ml) was heated in an oil-bath first at 140-45° for 1 hr and then at 180° for 6 hr, cooled and poured into crushed ice with vigorous stirring. Next day, the light brown solid that separated was collected, washed with water and crystallised from EtOH to get **6**.

7-Acetoxy-3-acetyl-6,8-bisdiphenylmethyl-2-methylchromone (**6a**): Light brown plates (250 mg), m.p. 161-62°; R_f 0.68 (solvent-B) (Found: C, 81.5; H, 5.7. $C_{40}H_{32}O_5$ requires C, 81.1; H, 5.4%); UV: 292 (3.54), 244 (4.12), 212 (4.59); IR: 1770, 1685 and 1590; PMR: 1.72 (*s*, 3H, $-CH_3$), 1.90 (*s*, 3H, $-OCOCH_3$), 2.31 (*s*, 3H, $-COCH_3$), 5.50 and 5.68 [2*s*, 1H each, $2\times -CH(Ph)_2$], 7.15 (*bm*, 20H, $4\times C_6H_5$) and 7.44 (*s*, 1H, C_5-H).

7-Acetoxy-3-acetyl-8-diphenylmethyl-2-methylchromone (**6c**): Light brown plates (300 mg), m.p. 141-42°; R_f 0.46 (solvent-B) (Found: C, 76.3; H, 5.5. $C_{27}H_{22}O_5$ requires C, 76.1; H, 5.2%); UV: 290 (3.44), 244 (4.03) and 214 (4.47); IR: 1765, 1695, 1635, 1605 and 1575; PMR: 1.92 (*s*, 3H, $-CH_3$), 2.29 (*s*, 3H, $-OCOCH_3$), 2.61 (*s*, 3H, $-COCH_3$), 6.11 [*s*, 1H, $-CH(Ph)_2$], 7.26 (*bm*, 10H, $2\times C_6H_5$), 7.45 (*d*, $J=10$ Hz, 1H, C_6-H) and 8.18 (*d*, $J=10$ Hz, 1H, C_5-H).

7-Acetoxy-3-acetyl-6-diphenylmethyl-2-methylchromone (**6a**): Light brown plates (300 mg), m.p. 105-6°; R_f 0.52 (solvent-B) (Found: C, 76.4; H, 5.4. $C_{27}H_{22}O_5$ requires C, 76.0; H, 5.2%); UV: 292 (3.53), 244 (4.10), 216 (4.53); IR: 1760, 1680, 1600, 1570; PMR: 1.90 (*s*, 3H, $-CH_3$), 2.30 (*s*, 3H, $-OCOCH_3$), 2.32 (*s*, 3H, $-COCH_3$), 5.53 [*s*, 1H, $-CH(Ph)_2$], 6.87 (*s*, 1H, C_8-H), 7.02 (*bm*, 10H, $2\times C_6H_5$) and 7.20 (*s*, 1H, C_5-H).

Deacetylation of **6a**, **6c** *and* **6e**

The substrate (50 mg) was hydrolysed by adding it into small lots to a boiling solution of aq. Na_2CO_3 (10%, 15 ml) and finally refluxing the solution on a wire gauze for 2 hr. The resulting reddish brown solution was filtered and the clear filtrate acidified with cold dil. HCl. The solid thus separated was collected and crystallized from MeOH to get the deacetylated product.

6,8-Bisdiphenylmethyl-7-hydroxy-2-methylchromone (**6b**): Light brown plates (30 mg), m.p. 108-9° (d); R_f 0.34 (solvent-B) (Found: C, 85.5; H, 5.7. $C_{36}H_{28}O_3$ requires C, 85.5; H, 5.5%); UV: 300 (3.77), 250 (4.08) and 194 (4.60); IR: 3400, 1635 and 1565; PMR: 2.15 (*s*, 3H, $-CH_3$), 5.75 and 6.02 [2*s*, 1H each, $2\times -CH(Ph)_2$], 6.27 (*s*, 1H, C_3-H), 7.25 (*bm*, 20H, $4\times C_6H_5$) and 7.69 (*s*, 1H, C_5-H).

8-Diphenylmethyl-7-hydroxy-2-methylchromone (**6d**): Light brown plates (25 mg), m.p. 194-95°; R_f 0.10 (solvent-B) (Found: C, 80.9; H, 5.6. $C_{23}H_{18}O_3$ requires C, 80.7; H, 5.3%); UV: 292 (4.21), 246 (4.39) and 195 (4.48); IR: 3400, 1630 and 1550; PMR: 2.30 (*s*, 3H, $-CH_3$), 6.30 [*s*, 1H, $-CH(Ph)_2$], 6.71 (*s*, 1H, C_3-H), 7.15 (*bm*, 10H, $2\times C_6H_5$), 7.40 (*d*, $J=10$ Hz, 1H, C_6-H) and 8.02 (*d*, $J=10$ Hz, 1H, C_5-H).

6-Diphenylmethyl-7-hydroxy-2-methylchromone (**6f**): Light brown plates (25 mg), m.p. 259-60°; R_f 0.16 (solvent-B) (Found: C, 80.9; H, 5.4. $C_{23}H_{18}O_3$ requires C, 80.7; H, 5.3%); UV: 292 (4.09), 248 (4.25), 195 (4.68); IR: 3350, 1645, 1625, 1580; PMR: 2.59 (*s*, 3H, $-CH_3$), 5.80 [*s*, 1H, $-CH(Ph)_2$], 6.75 (*s*, 1H, C_3-H), 7.60 (*s*, 1H, C_8-H), 7.20 (*bm*, 10H, $2\times C_6H_5$) and 7.72 (*s*, 1H, C_5-H).

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Oxidation of 2′-Hydroxychalcones

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2′-Hydroxychalcones (Ia-f) or the isomeric flavanones (IIa-f) on refluxing in DMSO for 30 min in the presence of catalytic amount of iodine afford the corresponding flavones (III) in high yields. This method is quicker and appears to be of general applicability.

The conversion of 2′-hydroxychalcones into flavones by prolonged refluxing with SeO_2 in isoamyl alcohol[1], is time-consuming and is applicable in those chalcones which do not have free hydroxyl group other than at 2′-position. The Kostanecki[2] method of converting 2′-hydroxychalcones into flavones by the action of ethanolic alkali on chalcone dibromide has limited applications. The use of dimethyl sulphoxide (DMSO) as an oxidising agent for affecting this conversion has been reported by several workers[3-5]. However, the reagent DMSO-I_2 for the oxidation of 2′-hydroxychalcones to flavones has not been used so far, though recently iodine-DMSO-sulphuric acid system has been employed[6] for dehydrogenation of flavonoids. We have not observed that 2′-hydroxychalcones (I) or flavanones (II) when refluxed with DMSO in the presence of catalytic amount of I_2 give the corresponding flavones (III) in more than 80% yields.

2′-Hydroxychalcones (Ia-f) and flavanones (IIa-f) were prepared by known methods[7].

2′-Hydroxy-5′-methylchalcone (Ia, 0.01 mol) was suspended in DMSO (30 ml) and a crystal of iodine added to it. The mixture was refluxed for 10 min, cooled, diluted with water, the solid obtained filtered off, washed with 20% aq sodium thiosulphate and recrystallised from ethanol to furnish 6-methylflavone (IIIa), m.p. 125° (lit.[8], m.p. 125°); yield 82%. This was found to be identical in all respects (m.p., m.m.p., PMR and co-IR) with an authentic sample of the flavone prepared by acid-catalysed cyclization of 2-hydroxy-5-methyldibenzoylmethane[8]; PMR ($CDCl_3$): 2.50 (*s*, 3H, Ar-CH_3), 3.94 (*s*, 3H, OCH_3), 6.78 (*s*, 1H, heteroaromatic H), 6.9-8.1 (*m*, 7H, Ar-H).

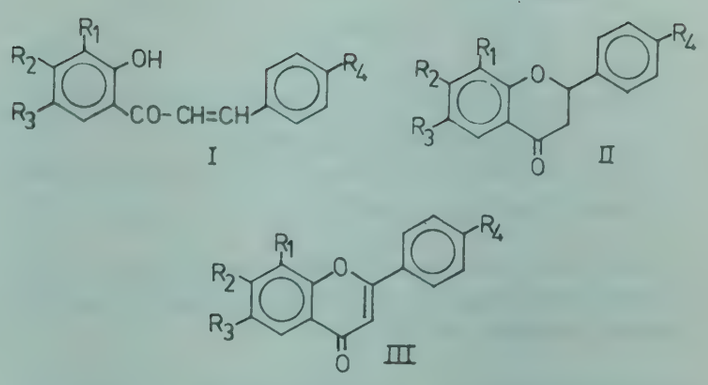

Table 1—Characterization Data of 2′-Hydroxychalcones (Ia-f), Flavanones (IIa-f) and Flavones (IIIa-f)

	R_1	R_2	R_3	R_4	m.p. (°C) I	m.p. (°C) II	m.p. (°C) III	% Yield of III from I	% Yield of III from II
a:	H	H	CH_3	H	99	105	125 (125)[9]	82	88
b:	H	H	CH_3	OCH_3	98	110	170 (170)[9]	87	90
c:	Br	H	CH_3	H	108	104	175 (175)[9]	82	84
d:	Br	H	CH_3	OCH_3	148	115	192 (192)[9]	85	90
e:	H	H	H	H	92	78	99 (99)[8]	84	86
f:	H	H	H	OCH_3	95	98	161-63 (161-63)[8]	85	87

Similarly, treatment of 2′-hydroxychalcones (Ib-f) or flavanones (IIa-f) gave corresponding flavones (IIIa-f), which are listed in Table 1.

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Synthesis of 3,4-Diaryl-2(5*H*)-furanones

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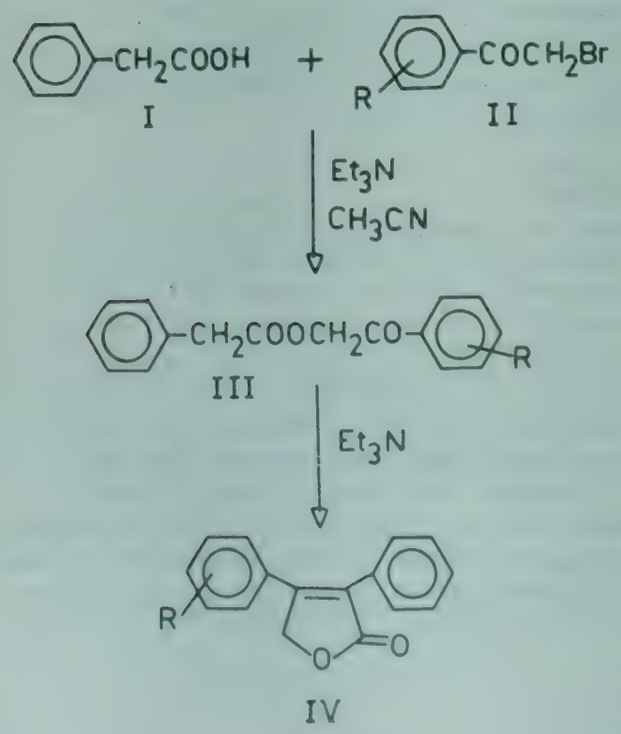
A simple and general two-step method for the synthesis of 3, 4-diaryl-2(5*H*)-furanones starting from phenylacetic acids and phenacyl bromides is described.

2(5*H*)-Furanones of $\Delta^{\alpha,\beta}$-butenolides are of much importance because of their antitumour, antifungal and antibacterial activities[1-3]. Several of them also occur in nature[3-5]. They are also useful intermediates in the synthesis of antileukamic lignan lactones[6]. Herein we report a simple, convenient and general route to 3, 4-diaryl-2(5*H*)-furanones from phenylacetic acids and phenacyl bromides (Scheme 1).

When phenylacetic acid (I) was refluxed for about 6 hr with *p*-bromophenacyl bromide (II) in acetonitrile in the presence of triethylamine, 3-phenyl-4-*p*-bromophenyl-2(5*H*)-furanone (IV) was obtained in 27% yield. However, when the intermediate (III) was isolated and refluxed with triethylamine in acetonitrile, the yield of the butenolide increased to 66%.



SCHEME 1

Table 1—Details of Phenacyl Esters (III) Prepared using Triethylamine

Ester	R	Yield[a] (%)	Reaction time (min)	m.p.[b] (°C)
1	*p*-Br	66	5	88 (89)[9]
2	*p*-Cl	69	10	85-86 (85-86)[12]
3	*m*-Cl	75	10	48-49 (48-49)[12]
4	*p*-NO_2	88	3	86 (86)[12]
5	*m*-NO_2	82	3	45-47 (45-47)[12]
6	*p*-Ph	82	20	88 (88.2-88.9)[10]
7	H	75	20	50 (50)[9]

[a]Isolated yields; and [b]melting points are uncorrected.

The intermediate substituted phenacyl esters (III) were prepared from phenylacetic acid and substituted phenacyl bromides using triethylamine and are listed in Table 1. The various $\Delta^{\alpha,\beta}$-butenolides (IV) prepared by the cyclisation of III in the presence of triethylamine in acetonitrile are listed in Table 2. These butenolides were fully characterised by their analytical and spectral (UV, IR, PMR and mass) data (Table 2). The infrared spectra (KBr) indicate that the carbonyl absorptions are characteristic of $\Delta^{\alpha,\beta}$-butenolides. The UV spectral data of all the lactones reveal the same pattern of absorptions at 243 and 290 nm in $CHCl_3$ solution.

It should be pointed out that simple phenacyl phenylacetate did not cyclise under the above conditions[7], but cyclisation of this ester could be achieved by treating the ester with Triton-B in acetonitrile at room temperature.

It is interesting to observe that *p*-nitrophenylacetic acid undergoes ready cyclisation at room temperature with *p*-bromophenacyl bromide to 3-*p*-nitrophenyl-4-*p*-bromophenyl-2(5*H*)-furanone in the presence of triethylamine[8]. The cyclisation was so facile that the intermediate phenacyl ester could not be isolated. However, when the reaction was carried out in benzene *p*-bromophenacyl *p*-nitrophenylacetate could be isolated in 71% yield.

p-Bromophenacyl phenylacetate (III)

Phenylacetic acid (0.15 g, 1.1 mmol) was dissolved in acetonitrile (10 ml) containing triethylamine (1 ml) and to this was added *p*-bromophenacyl bromide (0.28 g, 1 mmol) with stirring at room temperature. The reaction was complete within 5 min. It was allowed to stand for 1 hr, extracted with dichloromethane, washed successively with 2*N*-hydrochloric acid, 5% aq. sodium bicarbonate and water and the solvent was evaporated to give the ester; yield 0.22 g (66%); m.p. 88

Table 2 — Details of $\Delta^{\alpha,\beta}$-Butenolides (IV) Prepared by Cyclisation of Phenacyl Esters (III) using Triethylamine

Product	R	Reaction time (hr)	Isolated yield (%)	m.p.[a] (°C)	PMR ($CDCl_3$/TMS_{int}) (δ ppm)	Mol. formula (M^+)	Found (Calc.), %	
							C	H
1	*p*-Ph	8	39	178-79	8-7.3 (*m*, 14H); 5.22 (*s*, 2H)	$C_{22}H_{15}O_2$ (312)	84.10 (84.62)	4.98 (5.13)
2	*p*-Cl	6	64	113-14	7.6-7.1 (*m*, 9H); 5.20 (*s*, 2H)	$C_{16}H_{11}O_2Cl$ (272, 270)	69.82 (70.98)	4.14 (4.07)
3	*m*-Cl	6	56	63	7.5-7 (*m*, 9H); 5.1 (*s*, 2H)	$C_{16}H_{11}O_2Cl$ (272, 270)	69.82 (70.98)	4.14 (4.07)
4	*p*-NO_2	3	51	195-96	8.4-7 (*m*, 9H); 5.2 (*s*, 2H)	$C_{16}H_{11}NO_4$[b] (281)	67.58 (68.33)	4.05 (3.91)
5	*p*-Br	6	66	138-39	8.3-7 (*m*, 9H); 5.2 (*s*, 2H)	$C_{16}H_{11}O_2Br$ (316, 314)	60.16 (60.95)	3.45 (3.49)
6**	*m*-NO_2	3	49	136-37	—	$C_{16}H_{11}NO_4$[c] (281)	67.71 (68.33)	3.85 (3.91)

[a]Melting points are uncorrected; [b]N found (Calc.): 4.9 (5.0%); [c]N found (Calc.): 4.9 (5.0%).

(lit.[9], 89°); IR (CCl_4): 1750, 1710 cm^{-1}; UV (CH_3CN): 212 nm (ε 14919), 225 nm (ε 19693).

3-*Phenyl*-4-*p*-*bromophenyl*-2(5*H*)-*furanone*

p-Bromophenacyl phenylacetate (0.333 g, 1 mmol) was refluxed for 6 hr in acetonitrile (15 ml) containing triethylamine (1 ml). The reaction mixture was extracted with dichloromethane, washed successively with 2 *N*-hydrochloric acid and water, dried (Na_2SO_4) and the solvent evaporated to give the product, which was further purified by eluting through a column of silica gel (ACME, mesh: 60-120) with benzene; yield 0.206 g (66%); m.p. 136-38°; IR (KBr): 1760-1740 cm^{-1} (CO); UV ($CHCl_3$): 244 (ε 101107), 297 nm (ε 18175).

3,4-*Diphenyl*-2(5*H*)-*furanone*

Phenacyl phenylacetate (0.254 g, 1 mmol) was treated with Triton-B (0.5 ml) in acetonitrile (10 ml) and allowed to stand for 40 min with occasional shaking. It was extracted with dichloromethane, washed successively with 2*N*-hydrochloric acid and water, dried (Na_2SO_4) and the solvent evaporated to give the product, which was purified by eluting through a column of silica gel with benzene; yield 0.145 g (61%); m.p. 114-16° (lit.[11] 115-16°); IR (KBr): 1750-1640 cm^{-1} (CO).

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Isothiocyanate-Mediated Condensation of N-Acyl-α-amino Acids with Aromatic Aldehydes: One-Pot Synthesis of 1,2-Disubstituted 4-Arylmethylene-2-imidazolin-5-ones

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N-Acetyl/benzoyl-amino acids (**1c**/**1b**, **d**) when heated with isothiocyanates (**2**) in the presence of suitable aromatic aldehydes (**3**) with pyridine as a catalyst, afford 1, 2-disubstituted 4-arylmethylene-2-imidazolin-5-ones (**6**). However, N-benzyloxycarbonylaminoacetic acid (**1a**) gives the corresponding anilide (**11a**). Mechanisms of these reactions are discussed.

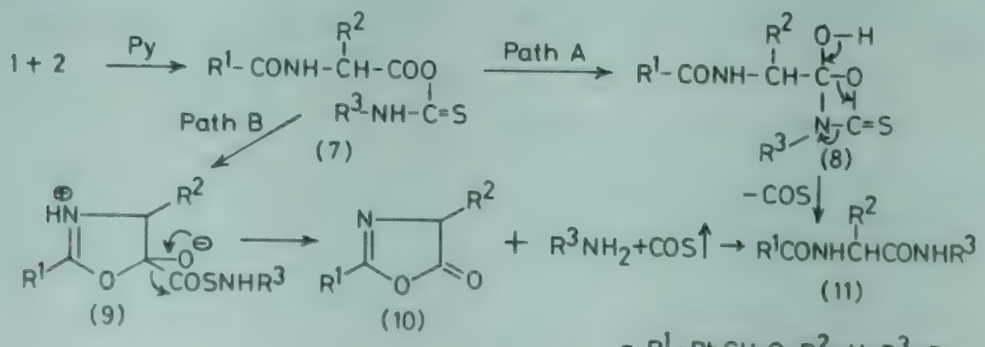
In continuation of our work on isothiocyanates[1,2] we have now studied the reaction of N-acyl-α-amino acids (**1**) with alkyl/aryl isothiocyanates (**2**) in the presence of some aromatic aldehydes using pyridine as a catalyst.

Whereas **1b** and **1c** afforded azlactone-based products (Table 1), **1a** gave only **11a** on reaction with phenyl isothiocyanate (**2a**) apparently via path-A (Scheme 1). The reaction of **1b** with 1-butyl isothiocyanate (**2b**), however, led to the formation of **4a** and **5e**, the latter undergoing cyclisation to **6e** only on prolonged heating *in vacuo* above its melting point[3] or by boiling in gl. acetic acid in the presence of freshly fused sodium acetate[4]. In all other cases, except cinnamaldehyde, (*Z*)-2-imidazolin-5-ones (**6**) were the major products, though (*Z*)-azlactones (**4**), (*Z*)-alkenamides (**5**) and/or N-substituted N-acyl-α-aminoacylamides (**11**) were also obtained in trace amounts in some of the reactions. It is worth noting that in the presence of salicylaldehyde, hippuric acid

Table 1—Results of the Reaction Between N-Acyl-α-amino Acids (**1**), Alkyl/aryl isothiocyanates (**2**) and Aromatic Aldehydes (**3**)

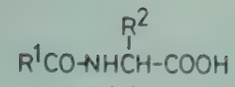
Reactants	Products[a]	Yield (%)	m.p. (°C)	
			Found	Reported
1a + **2a** + **3a**	**11a**	35(62)[b]	141-43	[g]
1b + **2a** + **3a**	**5a**	5	232-34	230-32[7]
	6a	52(57)[c]	179-80	180[8]
	11b	8	210-12	214[9]
1b + **2a** + **3b**	**5b**	16	260-62	[h]
	6b	37	190-92	[i]
1b + **2a** + **3c**	**4c**	13	214-15	216-17[10]
	6c	43	250-52	[j]
	11b	8	210-12	214[9]
1b + **2a** + **3d**	**11b**	10	210-12	214[9]
1b + **2b** + **3a**	**4a**	26	165-67	165[11]
	5e	27	189-90	188-90[12]
1c + **2a** + **3a**	**5g**	2	226-28	230[13]
	6g	7(30)[d]	239-40	240-41
1d + **2a** + **3e**	**11c**	5	169-70	169-70[1]
	12	[e]		
2c + **14**	**4a**	12	165-67	165[11]
	5d	69	192-94	188-89[15]
	or **6d**	32[f]	134-35	135[15]

[a] Except in the reaction of **1a**, formation of the corresponding azlactone was detected by TLC (silica gel/benzene) in all the cases.
[b] Obtained by aminolysis of mixed anhydride.
[c] Obtained on heating the reactants for 1 hr.
[d] Obtained on taking 2 mol of benzaldehyde.
[e] Detected by co-TLC (silica gel/benzene) with authentic specimen[5].
[f] It was obtained when the reactants were first heated at 130-40° for 30 min and subsequently at 160-70° for 30 min.
[g] For elemental analysis see text.
[h] The compound could not be obtained analytically pure, but on cyclisation afforded **6b** which gave correct elemental analysis.
[i] Found: C, 71.8; H, 4.4; N, 11.2. $C_{22}H_{15}N_3O_3$ requires C, 71.5; H, 4.1; N, 11.4%.
[j] Found: C, 78.2; H, 5.9; N, 11.5. $C_{24}H_{21}N_3O$ requires C, 78.5; H, 5.7; N, 11.4%.



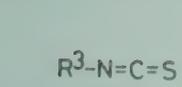
a. $R^1 = PhCH_2O$; $R^2 = H$; $R^3 = Ph$
b. $R^1 = Ph$; $R^2 = H$; $R^3 = Ph$
c. $R^1 = Ph$; $R^2 = Me$; $R^3 = Ph$
d. $R^1 = Me$; $R^2 = H$; $R^3 = Ph$

Scheme 1



(1)

a: R^1=$PhCH_2O$; R^2=H
b: R^1=Ph; R^2=H
c: R^1=Me; R^2=H
d: R^1=Ph; R^2=Me

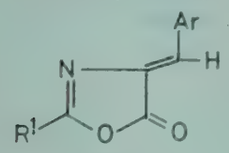


(2)

a: R^3=Ph
b: R^3=1-Bu
c: R^3=Me

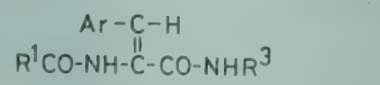
(3)

a: Ar=Ph
b: Ar=4-$O_2NC_6H_4$
c: Ar=4-$Me_2NC_6H_4$
d: Ar=Ph-CH=CH
e: Ar=2-HO-C_6H_4



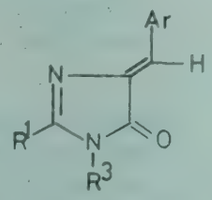
(4)

a: R^1=Ar=Ph
b: R^1=Ph; Ar=4-O_2N-C_6H_4
c: R^1=Ph; Ar=4 Me_2N-C_6H_4
d: R^1=Me; Ar=Ph
e: R^1=Ph-CH=CH; Ar=Ph
f: R^1=Ph; Ar=2-HO-C_6H_4

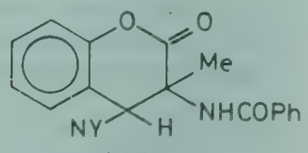


(5)

a: R^1=R^3=Ar=Ph
b: R^1=R^3=Ph; Ar=4-O_2N-C_6H_4
c: R^1=R^3=Ph; Ar=4-Me_2N-C_6H_4
d: R^1=Ph; R^3=Me; Ar=Ph
e: R^1=Ph; R^3=1-Bu; Ar=Ph
f: R^1=Me; R^3=Ar=Ph
g: R^1=Ph-CH=CH; R^3=Ar=Ph
h: R^1=Ph; R^3=Ph; Ar=2-HO-C_6H_4

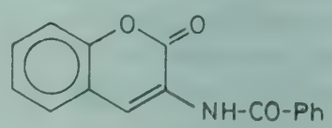


(6)



(12)

a, Y=O
b, Y=PhN



(13)

reacted with phenyl isothiocyanate to give **6h** and **13**[2].

It should be added that the reaction of **1c** with phenyl isothiocyanate in the presence of benzaldehyde afforded **6g**, the yield of which considerably improved on increasing the proportion of benzaldehyde.

Thermal cyclodehydration of **1** to **10** is ruled out since hippuric acid failed to undergo condensation with benzaldehyde on heating. Isothiocyanates on the other hand brought about cyclisation of **1** to **10** which underwent condensation with aldehyde present in the reaction mixture affording **4**. This was followed by aminolysis of **4** to **5** and cyclisation of **5** to **6**. Alternatively the free amine, liberated as a result of cyclocondensation of **1** with isothiocyanate, would combine with the aldehyde present to give schiff base which would react *in situ* with **10** to afford the unsaturated azlactone (**4**). To verify this possibility, **1d** and **2a** were heated in the presence of salicylaldehyde (**3e**) to give a mixture of products which could not be separated. However, **12a** and **12b** were discernible by TLC (silica gel/benzene) and these were identified by co-TLC with authentic specimens prepared by literature method[5]. This finding confirmed the generation of imine during the reaction. The formation of **11c** can be explained by aminolysis of **10** (Scheme 1) with the liberated aniline. Recently, a modified azlactone synthesis, using imines as synthons, has been reported[6]. The condensation of **10** with the imine would release free amine which would bring about aminolysis of the resultant azlactone (**4**) followed by cyclisation of the alkenamide (**5**) to give **6**.

The compounds reported here were characterised by their elemental analyses and spectral data and their identity was confirmed by comparison with authentic samples and/or by unambiguous synthesis.

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 720 spectrophotometer. Results of the present investigation and the relevant physical data are summarised in Table 1.

Reaction of phenyl isothiocyanate (**2a**) *benzaldehyde* (**3a**) *and benzyloxycarbonylamino-acetic acid* (**1a**): *Formation of benzyloxycarbonyl-aminoacetanilide* (**11a**)

A mixture of **1a** (0.418 g, 0.002 mol) **2a** (0.28 ml, 0.0024 mol), (0.2 ml, 0.002 mol) and pyridine (0.1 ml) was thoroughly mixed, heated at 160-70° for 30 min and was washed successively with pet. ether (40-60°), sodium bicarbonate solution and water. The residue was dissolved in hot benzene from which a solid separated out on cooling. It was filtered under suction and recrystallised from benzene to give **11a**, yield 0.2 g

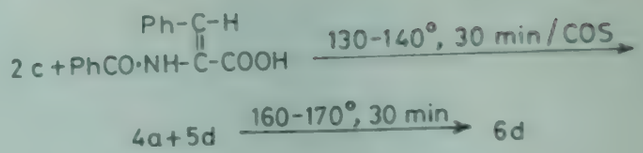
(35%), m.p. 141-43° (Found: C, 67.2; H, 5.9; N, 9.8. $C_{16}H_{16}N_2O_3$ requires C, 67.6; H, 5.6; N, 9.9%).

Reaction of N-acetyl/benzoyl-α-amino acids (**1c/1b, d**), *alkyl/aryl isothiocyanates* (**2**) *and aromatic aldehydes* (**3**): *Formation of* 4-*aryl-methylene-2-oxazolin-5-ones* (**4**), *N-substituted* 2-*acylaminocinnamides* (**5**) *and/or* 1,2-*disubstituted* 4-*arylmethylene-2-imidazolin-5-ones* (**6**)

The reaction was carried out in a similar mannèr as described above. From the benzene insoluble part, products **11** and **5** were obtained in trace amounts. The benzene filtrate was stripped of solvent under reduced pressure to afford **6** which was recrystallised from ethanol or benzene-ethanol. The results are given in Table 1.

Reaction of 2-*N-benzoylaminocinnamic acid* (**14**) *and methyl isothiocyanate* (**2c**): *Formation of* 4-*benzylidene-2-phenyl-2-oxazolin-5-one* (**4a**), *N-methyl* 2-*benzoylaminocinnamide* (**5d**) *and/or* 4-*benzylidene-1-methyl-2-phenyl-2-imidazolin-5-one* (**6d**)

The reactants were heated at 130-40° for 30 min and the reaction mixture was worked-up as usual to give **4a** and **5d**. When heating was continued for additional 30 min at 160-70°, **6d** was isolated instead of **5d**, along with some polymeric material.(Scheme 2).



Scheme 2

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Cyclisation of N-Substituted 2-Acylamino-2-alkenamides: Some Observations

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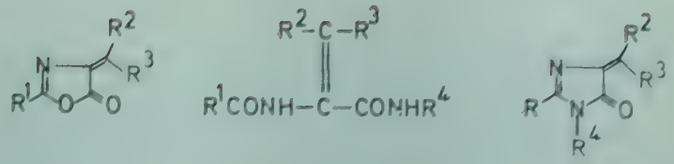
2-Acetylaminocinnamanilide undergoes cyclisation to afford **3a** in neutral, acidic and basic media. However, N-substituted 2-benzoylamino-3-aryl-2-alkenamides (**2b-f**) afford the corresponding 5-imidazolones (**3b-f**) only under neutral or acidic condition. Compound **2g** gives exclusively the azlactone **1g**.



	1	2		3
	R^1	R^2	R^3	R^4
a	Me	Ph	H	Ph
b	Ph	PhCH=CH	H	Ph
c	Ph	H	PhCH=CH	Ph
d	Ph	4-$Me_2NC_6H_4$	H	Ph
e	Ph	Ph	H	CH_2COOH
f	Ph	Ph	H	1-Bu
g	Ph	——$(CH_2)_5$——		Ph

Acetic acid-mediated cyclisation of **2a** has been reported to be unsuccessful[1], though conversion of **2** into **3** (R^1 and R^2 = aryl groups; R^3 = H) under similar conditions is known[2-5]. Some imidazolones (**3**) are potentially important as antibacterial[1] and antiinflammatory[6] agents and some of them may be useful in polymer chemistry. It was therefore thought worthwhile to critically examine the synthesis of imidazolones starting from N-substituted 2-acylamino-2-alkenamides (**2**), particularly with references to the substituent effect, stereochemistry and reaction conditions.

As already reported[2], the substituents at C-2 and 4-C=C positions as well as the type of amine play an important role in the cleavage of the 1,5-bond of **1**.

The alkenamides (**2a-f**) afforded the corresponding 5-imidazolones (**3a-f**), and the reaction was faster in acetic acid in comparison to neutral medium . Contrary to the earlier report[1], we have observed that **2a** cyclises to **3a**, on heating in gl. acetic acid. None of the alkenamides (**2**), except **2a** which gave **3a** in a very good yield, cyclised to **3** in boiling pyridine.

Though aminolysis of **1b** and **1c** has been found to be stereospecific[2], the cyclisation of the corresponding alkenamides afforded only the (*Z*)-imidazolone (**3b**). Since **2b** and **2c** are highly stable, formation of **3b** should be accounted for the isomerisation of **3c** which, like **1c**, appears to be thermolabile.

It has been found that **2f** affords **1f**, besides **3f** and **2g** gives only **1g**. The formation of 5-imidazolones (**3**) and/or 5-oxazolones (**1**) can be rationalysed by invoking structures in the light of Baldwin's rules[8].

Products obtained in the present study were characterised by spectral data and elemental analyses.

All melting points reported are uncorrected. IR and UV spectra were recorded on Perkin-Elmer 720 and Cary-14 spectrophotometers respectively. Relevant physical data are presented in Table 1.

Table 1—Cyclisation Products of N-Substituted 2-Acylamino-2-alkenamides (**2**)

Product*	Method	Yield (%)†	m.p. (°C)	
			Found	Reported
1f	C	2	163-65	165-66[10]
1g	C	50	138-40	137-38[12]
3a	A	23	144-45	144[9]
	B	80	144-45	—
3b‡	A	44	197-98	—
3d**	A	44	250-52	—
3e	A	17	203-204	200-202[13]
3f	C	16.5 (33)	97-99	99[11]

*Some of the imidazolones reported here were prepared earlier by prolonged heating, often under vacuum, of the corresponding alkenamides above their melting points.

†In some of the cases, considerable amount of starting material was recovered and the actual conversion is higher as given in parentheses for the compound **3f**.

‡Pure **1c** as well **1b**[14] gave the same product (Found: C, 82.0; H, 5.1; N, 7.9. $C_{24}H_{18}N_2O$ requires C, 82.3; H, 5.1; N, 8.0%); UV (95% EtOH): 240, 275 and 395 nm (log ε 1.06, 0.77 and 4.03 respectively).

For its preparation, **1d was generated in benzene following literature method[14], filtered, concentrated and without isolation was used for the reaction; yield based on hippuric acid taken (Found: C, 78.2; H, 5.9; N, 11.5. $C_{24}H_{21}N_3O$ requires C, 78.5; H, 5.7; N, 11.4%); UV (95% EtOH): 275 and 470 nm (log ε 1.43 and 3.5 respectively).

4-Benzylidene-2-methyl-1-phenyl-2-imidazolin-5-one (**3a**): *Method A, a typical procedure for preparation of 5-imidazolones* (**3**)

Aminolysis of **1a** with aniline and cyclisation of the resultant anilide (**2**) were carried out in gl. acetic acid

according to the procedure published earlier[2]. The product was purified by TLC (silica gel./methylene chloride), yield 23%, m.p. 144-45° (lit.[9], m.p. 144°).

Method B

4-Benzylidene-2-methyl-2-oxazolin-5-one (**1a**; 0.38 g, 0.002 mol) and aniline (0.24 ml; 0.0024 mol) were taken in dry pyridine (5 ml) and the mixture was heated under reflux for 4 hr, cooled and poured into crushed ice with constant stirring. The precipitate was filtered under suction, washed with cold water and crystallised from aq. ethanol, yield 0.41 g (80%), m.p. 144-45° (lit.[9], m.p. 144°).

Cyclisation of N^1-Butyl-α-benzoylaminocinnamide (**2f**): *formation of* **1f** *and* **3f**: *Method C, a typical procedure for preparation of* 5-*imidazolones* (**3**)

The amide **2f** (0.32 g, 0.001 mol) and freshly fused sodium acetate (0.1 g) were taken in gl. acetic acid (10 ml) and the mixture was heated under reflux for 4 hr and worked-up as usual. The crude product was extracted with hot benzene and filtered. The benzene soluble part was purified by TLC (silica gel/benzene) to afford **1f**, yield 0.005 g (2%; actual conversion 4%), m.p. 163-65° (lit.[10], m.p. 165-66°) and **3f**, yield 0.05 g (16.5%, actual conversion 33%), m.p. 97-99° (lit.[11], m.p. 99°).

Cyclisation of N^1-phenyl-2-benzoylamino-2-cyclohexylideneacetamide: formation of **1g**

The title reaction was carried out according to method C. The benzene extract was concentrated to dryness and triturated with ethanol to give **1g**, yield 50%, m.p. and m.m.p. 138-40° (lit.[12], m.p. 137-38°).

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A Novel Synthesis of Perhydropyrimidine-2-thiones

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Cinnamoyl isothiocyanate (**1**) reacts with amines (aniline, *p*-toludine, benzylamine) to give the corresponding cinnamoylthiourea derivatives (**2a-c**). Compounds **2a-c** undergo cyclization when refluxed with sodium ethoxide solution to give the corresponding perhydropyrimidine derivatives (**3a-c**). Compound **1** also reacts with cyanoacetic hydrazide or 3-amino-2-pyrazolin-5-one to give one and the same product, identified as cinnamoylthiourea derivative (**8**). Cyclization of **8** affords the corresponding perhydropyrimidine derivative (**9**).

Pyrimidine derivatives are biologically important products and their synthesis and chemistry have received considerable attention[1-3]. In spite of this, literature inspection reveals that relatively few perhydropyrimidine-thiones have been synthesised and no general, simple and efficient route for their synthesis is available[4,5]. In the present investigation we report a new general route for the synthesis of these derivatives via the reaction of cinnamoyl isothiocyanate (**1**) and amines. Thus, compound **1** reacted with aniline, *p*-toludine and benzylamine in refluxing acetone to yield the corresponding cinnamoylthioureas (**2a-c**), the structures of which were established by elemental analyses, IR and PMR data (Table 1). These compounds (**2a-c**) underwent cyclization when refluxed in sodium ethoxide solution to give products that could be formulated as perhydropyrimidine derivatives (**3**) or the thiazines (**4**). The pyrimidine structure (**3**) was considered more likely, based on the stability of the reaction products under conditions reported to effect ready opening of thiazines (Chart 1). The PMR spectra were also in agreement with the proposed perhydropyrimidine structure **3** (Table 1). The structure **3** received further support from the ready conversion of **3a** into the corresponding oxygen-counter analogue **3d** by boiling with H_2O_2 in the presence of acetic acid[6].

Compound **1** also reacted with cyanoacetic hydrazide to yield the thiosemicarbazide 1:1 adduct. Firstly we thought the product to be the thiosemicarbazide **5**. However, this structure was readily ruled out as the same product was obtained on treatment of 3-amino-2-pyrazolin-5-one (**6**) with **1**. Thus, structure **7** or **8** was considered for the product

Table 1—Characterization Data of Compounds **2a-c**, **3a-d**, **8** and **9**

Compd	Colour	Crystallized from	m.p. °C	Yield (%)	Mol. formula*
2a	Colourless crystals	C_6H_6	151	85	$C_{16}H_{14}N_2OS$
2b†	Pale yellow needles	Me_2CO	195	80	$C_{17}H_{16}N_2OS$
2c	Yellow needles	Me_2CO	180	80	$C_{17}H_{16}N_2OS$
3a	Colourless crystals	C_6H_6	179	75	$C_{16}H_{14}N_2OS$
3b‡	Colourless crystals	EtOH	163	65	$C_{17}H_{16}N_2OS$
3c	Colourless crystals	EtOH	154	50	$C_{17}H_{16}N_2OS$
3d	Pale yellow	EtOH	260	60	$C_{16}H_{14}N_2O_2$
8	Yellow powder	Me_2CO	184	85	$C_{13}H_{12}N_4O_2S$
9**	Pale yellow crystals	Me_2CO	163	60	$C_{13}H_{12}N_4O_2S$

*All compounds gave satisfactory elemental analyses (C, H, N).
†PMR: δ 2.4 (*s*, 3H, CH_3), 7.4-8.0 (*m*, 13H, Ar$-H$, ylidenic CH and 2NH protons).
‡PMR: δ 2.4 (*s*, 3H, CH_3), 3.4-4.0 (*m*, 3H, CH and CH_2), 6.7 (*s*, 1H, NH), 7.3-7.6 (*m*, 9H, Ar$-H$).
**PMR: δ 2.3 (*s*, 2H, CH_2), 3.6-3.9 (*m*, 3H, 3NH), 7.3-7.9 (*m*, 7H, Ar$-H$ and ylidenic CH protons).

(Chart 2). The PMR agreed with the proposed structure **8** and exhibited signals at δ 2.3 (*s*, 2H, CH_2); 3.6-3.9 (*m*, 3H, 3NH), 7.3-7.9 (*m*, 7H, Ar$-H$ and ylidenic CH protons). If structure **7** was assigned to the product, no signal would have appeared for $-CH_2$ protons in its PMR spectrum.

Cyclization of **8** in sodium ethoxide solution led to the formation of the corresponding perhydropyrimidine derivative **9** (Chart 2).

All the compounds described here were obtained in excellent yields and thus the present method constitute a general route for the synthesis of perhydropyrimidines.

Melting points are uncorrected. IR (KBr) spectra were recorded on a Schmatzu 408 spectrophotometer and 60 MHz PMR spectra on an EM-360 spectrometer in DMSO.

Cinnamoylthiourea derivatives (**2a-c** *and* **8**)

A solution of ammonium thiocyanate (1 mol) in acetone (30 ml) was refluxed for 15 min and cinnamoyl chloride (1 mol) added to it. After refluxing the mixture for 15 min, the appropriate amine (aniline, *p*-toludine, benzylamine or cyanoacetic hydrazide or amino-

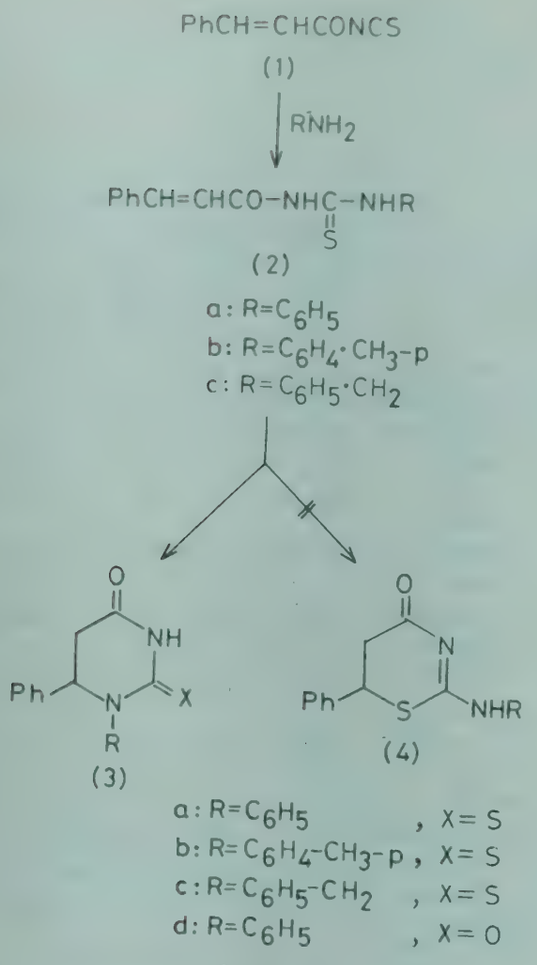

Chart 1

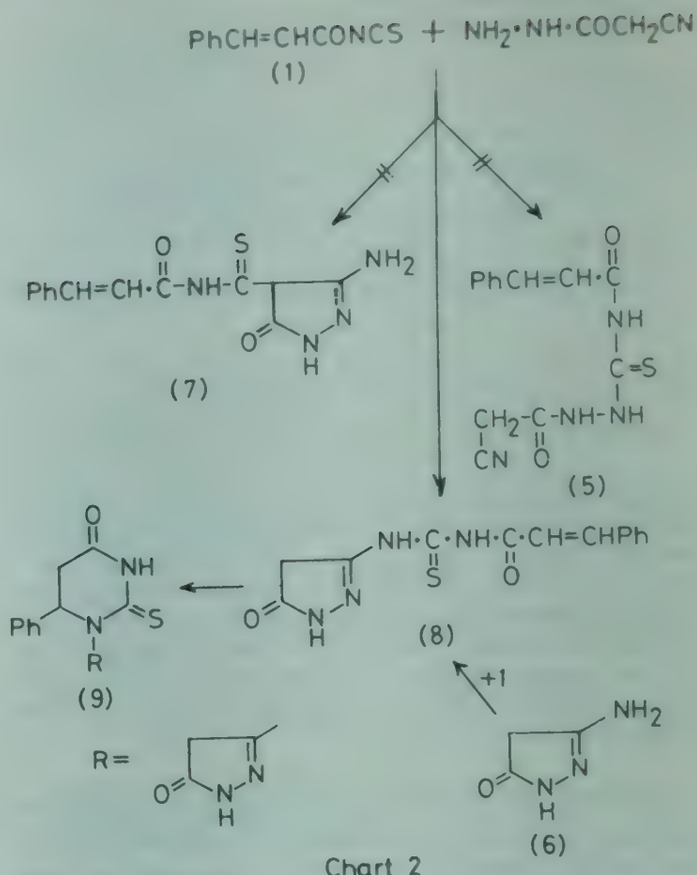

Chart 2

pyrazolone) (1 mol) was added to it and the reaction mixture refluxed for 1 hr, cooled, poured into ice-water and the separated solid filtered and crystallized from a suitable solvent to give **2** or **8** (Table 1).

Perhydropyrimidine-thiones (**3a-c** *and* **9**)

Compound **2** or **8** (0.01 mol) was dissolved in sodium ethoxide solution (0.01 mol sodium in 30 ml ethanol) and the solution refluxed for 1 hr, cooled, poured into cold water and neutralized with dil. hydrochloric acid. The separated solid was filtered, washed with water and crystallized from a suitable solvent to give **3** or **9** (Table 1).

Preparation of **3d**

A solution of **3a** (1 g) in acetic acid (10 ml) and H_2O_2 (2 ml) was boiled under reflux for 1 hr, cooled and neutralized with sodium carbonate solution. The resultant solid was filtered, washed with water and crystallized from ethanol (Table 1).

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Newer Piperazinothiazolidinones & Azetidinones†

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Reaction of substituted benzaldehyde 4-(4-phenyl-1-piperazinyl/anilino-carbonylmethyl)-3-thiosemicarbazones (Ia-f) with thioglycolic acid and chloroacetyl chloride affords the corresponding five membered thiazolidinone (IIa-e) and four membered azetidione derivatives (IIIa-f) respectively.

Thiosemicarbazone moiety has not been utilized as yet in the synthesis of thiazolidinones and azitidinones which are well known biologically active compounds[1-5].

In the present study one of the nitrogens of the thiosemicarbazone moiety has been converted into the five membered thiazolidinones and four membered azetidinones. Their structures were established by elemental analyses and spectral data.

The required substituted benzaldehyde 4-(4-phenyl-1-piperazinyl/anilino-carbonylmethyl)-3-thiosemicarbazones (Ia-f) were prepared by the reaction of chloroacetamides[6] with benzaldehyde thiosemicarbazones in basic medium. The chloroacetamides in turn were prepared from aryl amines[7,8] and chloroacetyl chloride. Compounds I were converted into the desired thiazolidenones (IIa-e) and azetidinones (IIIa-f) (Table 1) by reaction with thioglycolic acid and chloroacetyl chloride respectively, as shown in Scheme 1.

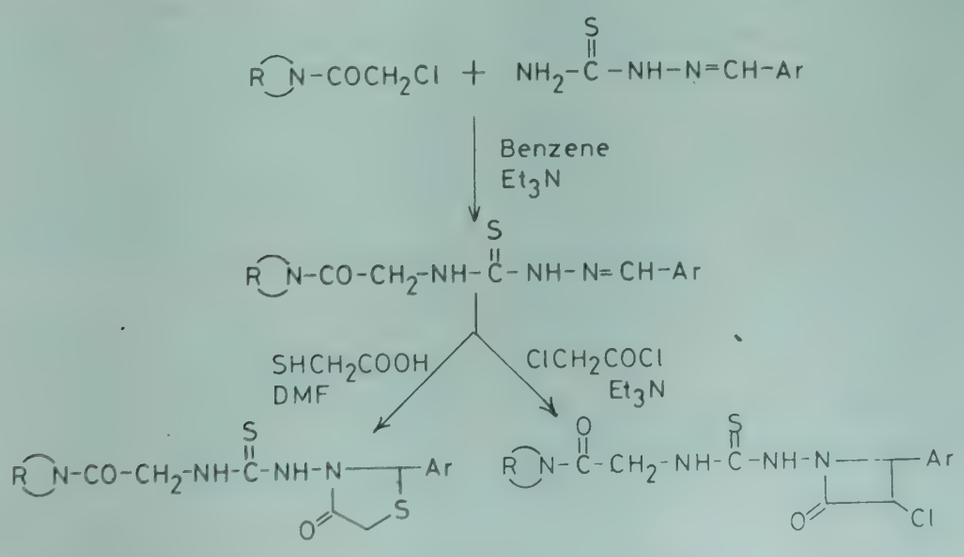
Melting points were taken in open capillary tubes and are uncorrected. Purity of compounds was routinely checked by TLC on silica gel G. IR spectra were recorded in KBr on a Perkin-Elmer Infracord spectrophotometer (ν_{max} in cm^{-1}) and mass spectra on a JMSD 300 instrument fitted with JMS 2000 data system at 70 ev.

Substituted benzaldehyde 4-(4-*phenyl*-1-*piperazinyl/anilino-carbonylmethyl*)-3-*thiosemicarbazones* (Ia-f)

A mixture of appropriate chloroacetamide (0.01 mol) and substituted thiosemicarbazone (0.01 mol) in dry benzene (40 ml) containing Et_3N (0.01 mol) was refluxed for 10 hr on a water-bath, solvent removed and the residue poured into ice cold water when a crystalline solid separated out. It was filtered and recrystallized from a suitable solvent to give I (Table 1). Compound Ia in its IR spectrum exhibited characteristic bands at 1680 (C=O) and 1070 (C=S).

2-*Aryl*-3-[3-(4-*phenyl*-1-*piperazinyl/anilino-carbonylmethyl*)-2-*thiouriedo*]-2-*thiazolidinones* (*II*)

To I (0.01 mol) in DMF (30 ml) was added thioglycolic acid (0.01 mol) and the reaction mixture refluxed for 10 hr containing a pinch of anhyd. $ZnCl_2$, cooled and poured into ice cold water when crystalline solid separated out. It was filtered, washed and recrystallized from DMF/water. The characterization



Scheme 1

† Part of the work will be incorporated in Ph.D. thesis of Vijai K Srivastava.

Table I – Characterization Data of Various Compounds Prepared

Compd	RN–	Ar	m.p.* °C	Mol. formula	N (%)†	
					Found	Calc.
Ia	4-Phenyl-1-piperazinyl	C_6H_5	218	$C_{20}H_{23}N_5OS$	19.3	19.4
Ib	4-Phenyl-1-piperazinyl	4-$N(CH_3)_2C_6H_4$	160	$C_{22}H_{28}N_6OA$	19.8	19.8
Ic	4-Phenyl-1-piperazinyl	4-OCH_3.C_6H_4	245	$C_{21}H_{25}N_5O_2S$	17.0	17.0
Id	Anilino	C_6H_5	220	$C_{16}H_{16}N_4OS$	18.0	17.9
Ie	Anilino	4-$N(CH_3)_2C_6H_4$	195	$C_{18}H_{21}N_5OS$	18.7	18.7
If	Anilino	4-OCH_3.C_6H_4	250	$C_{17}H_{18}N_4O_2S$	16.4	16.2
IIa	4-Phenyl-1-piperazinyl	C_6H_5	160	$C_{22}H_{25}N_5O_2S_2$	15.4	15.5
IIb	4-Phenyl-1-piperazinyl	4-$N(CH_3)_2C_6H_4$	300	$C_{24}H_{30}N_6O_2S_2$	16.9	16.9
IIc	4-Phenyl-1-piperazinyl	4-OCH_3.C_6H_4	225	$C_{23}H_{27}N_5O_3S_2$	14.1	14.1
IId	Anilino	C_6H_5	300	$C_{18}H_{23}N_5O_2S_2$	18.1	18.1
IIe	Anilino	4-OCH_3.C_6H_4	200	$C_{19}H_{20}N_3O_3S_2$	16.8	16.8
IIIa	4-Phenyl-1-piperazinyl	C_6H_5	110	$C_{22}H_{24}N_5O_2SCl$	15.3	15.3
IIIf	4-Phenyl-1-piperazinyl	4-$N(CH_3)_2C_6H_4$	130	$C_{24}H_{29}N_6O_2SCl$	16.8	16.8
IIIc	4-Phenyl-1-piperazinyl	4-OCH_3.C_6H_4	90	$C_{23}H_{26}N_5O_3SCl$	14.3	14.3
IIId	Anilino	C_6H_5	130	$C_{18}H_{17}N_4O_2SCl$	14.4	14.4
IIIe	Anilino	4-$N(CH_3)_2C_6H_4$	150	$C_{20}H_{22}N_5O_2SCl$	16.2	16.2
IIIf	Anilino	4-OCH_3.C_6H_4	195	$C_{19}H_{19}N_4O_3SCl$	13.4	13.4

* Compounds I and II were crystallized from DMF-H_2O and III from dioxane-H_2O.
† Satisfactory C and H analyses were obtained for all the compounds.

data of the compounds thus synthesized are given in Table 1. The IR spectrum of IIa showed characteristic peaks at 1680 (C=O), 1070 (C=S), 2850 (C=N).

In the mass spectrum of IIa the molecular ion appeared at *m/z* 498 with low intensity (5%) indicating lesser stability of the compound. The molecular ion lost the elements of $COCH_2$ to give fragments *m/z* 161 (10%) and 295 (90%). The M^+ also underwent cleavage of the bond between C=S and NH attached to the thiazolidinone ring to give fragements at *m/z* 262 (20%) and 236 (10%). The ion at *m/z* 262 underwent further fragmentation to yield phenylpiperazine acylium ion *m/z* 189 (15%) which ultimately gave rise to phenylpiperazine ion *m/z* 161 (30%) by losing a CO radical.

The *m/z* 161 ion disenigrated to yield the ion at *m/z* 132 (10%) which further lost one ethylene molecule to give the ion at *m/z* 104 (10%). It ultimately formed phenyl cation (*m/z* 77; 10%). On the other hand the phenylpiperazine cation (*m/z* 161) ejected out a nitrogen atom to give the *m/z* 147 (20%) ion which in turn lost one ethylene molecule to form phenylaziridine cation (*m/z* 119; 50%). This ion lost a methene radical to give $C_6H_5-N=CH_2^+$ ion (*m/z* 105; 10%) which underwent successive losses of a methene radical and nitrogen atom ultimately producing the phenyl cation.

The ion *m/z* 295 consisting of a thiazolidinone ring might undergo disentigration via two routes. In the first route it can split into *p*–N,N-dimethylaminophenyl cation (*m/z* 120; 150%) and *m/z*175 (20%) ion. The latter may undergo successive deprotonation followed by rupture to yield ions at *m/z* 174 (25%), 173 (15%) and 72 (100%) respectively. The former produced ions at *m/z* 105 (10%), 90 (10%) and 76 (10%).

In the second route the fragment *m/z* 295 can undergo fragmentation to yield the *m/z* 251 (15%) ion which further undergoes successive deprotonation to form *m/z* 250 (12%) and 249 (25%) ions respectively. The latter ion disentigrates to yield *m/z* 72 (100%) and 177 (20%) ions. The latter undergoes successive deprotonation and fragmentation to form ions at *m/z* 176 (18%), 175 (20%) and 148 (20%). The ions *m/z* 72 produced by first and second routes jointly contribute to the base peak.

4-Aryl-3-chloro-1-[3-(4-phenyl-1-piperazinyl/anilinocarbonylmethyl)-2-thioureido]-2-azetidinones (IIIa-f)

To compound I (0.01 mol) in dioxane (50 ml) were added chloroacetyl chloride (0.01 mol) and Et_3N (0.1 mol) at 0° with shaking. The reaction mixture was left at room temperature for 3 hr and then refluxed for 10 hr, excess of solvent distilled off, and the concentrate poured inoto ice water where upon a solid separated out which was filtered, washed and recrystallized from a suitable solvent to give III. The characterization data of the compounds thus synthesised are given in Table 1; IR: 1760 (C=O of monocyclic β lactone) 1070 (C=S).

The mass spectrum of IIIb showed the M^+ at *m/z* 501 (5%) and its isotopic peak (503, 2%). Fragmentation of M^+ gave rise to the ions at *m/z* 262 (100%) and 239 (10%) the latter ion contained azetidinone ring. The former ion underwent cleavage of $CO-CH_2$ bond to give the ion at *m/z* 199 (10%) which lost CO radical to form the phenyl piperazine cation (*m/z* 161, 20%). Successive losses of N, C_2H_5, CH_2 and CH_2 radicals from this ion produced ions at *m/z* 147 (50%), 119 (40%), 105 (30%) and 91 (20%). The last ion produced phenyl cation (*m/z* 77; 40%) by losing a nitrogen radical.

Removal of chloroketene radical from *m z* 239 ion yielded an ion at *m/z* 162 (10%) which on fragmentation produced ions at *m/z* 133 (30%), 120 (30%), 105 (30%) 90 (10%) and 76 (10%; benzyne cation) through the successive losses of HN^+-N, CH, $\dot{C}H_3$, $\dot{C}H_3$ and $\dot{N}$ units. The *m/z* 161 ion underwent fragmentation involving the loss of $\dot{C}H_2N$, $\dot{C}_2H_4$ and HCN radicals forming the ions at *m/z* 132 (65%) and 104 (20%) and the phenyl cation *m/z* 77 respectively.

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Synthesis & Spectral Studies of 2,3-Dihydro-2-aryloxy-1,3,2-oxazaphospholo[4,5-*b*]pyridine-2-oxides

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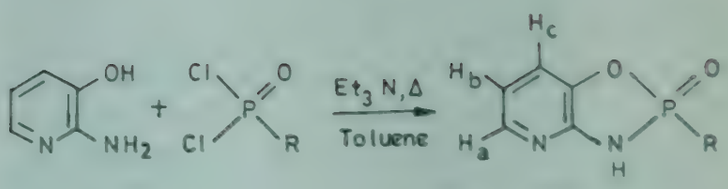
A series of 2,3-dihydro-2-aryloxy-1,3,2-oxazaphospholo[4,5-*b*]pyridine-2-oxides (**1**) have been synthesized and their structures elucidated by spectral studies (IR and PMR).

In view of the reports that organophosphorus compounds structurally related to purine possess promising antitumour activity[1,2], we have synthesized a series of the title compounds and characterised them from their spectral data.

The title compounds (**1a-f**) were synthesized by the condensation of 2-amino-3-hydroxypyridine with various aryloxyphosphorodichloridates or cyclohexylphosphonic dichloride in toluene in the presence of triethylamine. In general, the reaction was accomplished within 5 to 6½ hr at refluxing temperature and the yields were fairly good (58-71%). The physical and spectral data of the compounds thus synthesized are given hn Table 1.



1

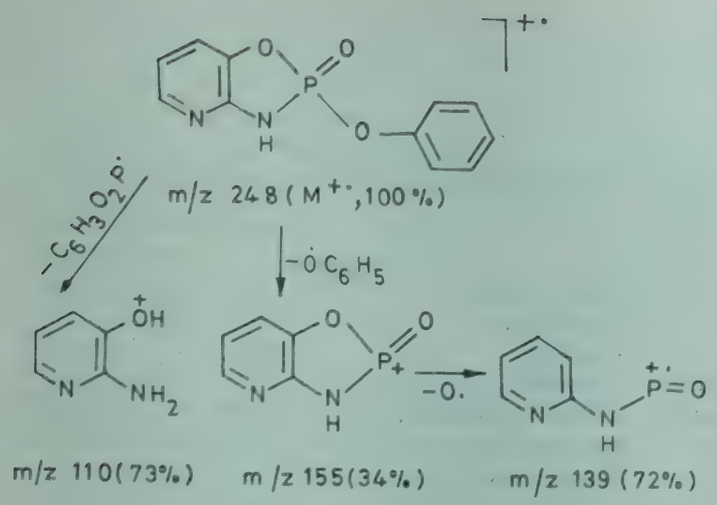
	R		R
1a	C_6H_5O	**1d**	4-Cl-C_6H_4O
1b	3-CH_3-C_6H_4O	**1e**	4-Cl-3CH_3-C_6H_3O
1c	3,5-$(CH_3)_2$-C_6H_3O	**1f**	C_6H_{11}

The high melting points (Table 1) and insolubility of **1a-f** in usual organic solvents may be attributed to the presence of hydrogen bonding[3] between phosphoryl oxygen and amidic hydrogen. This was substantiated by the appearance of $\nu_{P=O}$ and ν_{P-NH} in the regions[4,5] 1185-1204 and 3390-3430 cm^{-1} respectively (Table 1). Two characteristic bands for P−O−Ar function, one at 1258-1244 for Ar−O and the other at 970-930 cm^{-1} for P−O, appeared[5] in all the compounds. The PMR spectra of **1** were recorded in acetic acid-d_4 because of their poor solubility in other solvents. However, the N−H proton appeared as a broad signal ($W_{\frac{1}{2}}$ = 15 Hz) at about δ 8.50. The protons on the pyridine moiety (H_{a-c}) and other aromatic (or cyclohexyl) protons resonated in the usual range (Table 1).

The mass spectra of these compounds exhibited peaks corresponding to the fragments ($M^+ - OR$), *m/z*

Table 1 — Physical and Spectral Data of 2,3-Dihydro-2-aryloxy-1,3,2-oxazaphospholo[4,5-*b*]pyridine-2-oxides (**1a-f**)

Compd	Yield (%)	m.p. °C	Mol. formula	Found(%) (Calc.) C	H	PMR (δ, ppm)
1a	71	234(d)	$C_{11}H_9O_3N_2P$	53.2 (53.2)	3.9 (3.6)	6.50-8.25 (*m*, 8H, H_{a-c} and Ar-*H*), 8.50 (br, $W_{\frac{1}{2}}$ ~ 15 Hz, N−H).
1b	71	245(d)	$C_{12}H_{11}O_3N_2P$	54.8 (55.0)	4.5 (4.2)	2.23 (*s*, 3H, CH_3), 6.50-8.25 (*m*, 6H, H_{a-c} and Ar-*H*), 6.65 (*s*, 2'-H), 8.50 (br, $W_{\frac{1}{2}}$ ~ 15 Hz, N−H)
1c	58	224(d)	$C_{13}H_{13}O_3N_2P$	56.8 (56.5)	5.0 (4.7)	2.19 and 2.20 (2*s*, 3' and 5'-CH_3), 6.45 (*s*, 3H, 2'-, 4'- and 6'-H), 6.46-6.90 (*m*, 1H, H_b) 6.60-7.20 (*m*, 2H, H_a and H_c).
1d	67	229(d)	$C_{11}H_8O_3N_2PCl$	47.1 (46.7)	3.1 (2.8)	6.50-8.00 (*m*, 3H, H_{a-c}), 6.77 (*d*, 2H, J = 9 Hz, 2' and 6'-H), 7.14 (*d*, 2H, J = 9 Hz, 3' and 5'-H).
1e	66	239(d)	$C_{12}H_{10}O_3N_2PCl$	48.8 (48.6)	3.6 (3.4)	2.26 (*s*, 3H, 3'-CH_3), 6.57 (*d*, 1H, J = 7.6 Hz, 6'-H), 6.68 (*dd*, 1H, J = 8.4 Hz, 6.2 Hz, H_b), 6.72 (*s*, 1H, 2'-H), 7.12 (*d*, 1H, J = 8.4 Hz, H_c), 7.26 (*d*, 1H, J = 7.6 Hz, 5'-H), 7.48 (*d*, 1H, J = 6.1 Hz, H_a).
1f	67	190-92	$C_{11}H_{15}O_3N_2P$	52.3 (52.0)	6.2 (5.9)	1.00-2.00 (*m*, 11H, cyclohexyl-H), 6.92 (*dd*, 1H, J = 8.0, 6.2 Hz, H_b), 7.50 (*d*, 1H, J = 8.0 Hz, H_c), 7.66 (*dd*, 1H, J = 6.2, 1.3 Hz, H_a).



Scheme 1

139 and *m/z* 110 consistent with the structures proposed. The mass spectral fragmentation of **1a** is shown in Scheme 1. Appearance of the cation at *m/z* 155 (34%) with moderate intensity clearly indicates the presence of 1,3,2-oxazaphospholo[4,5-*b*]pyridine-2-oxide ring system in **1**.

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Beckmann IR 18A spectrophotometer, and PMR spectra in acetic acid-d_4 on a Varian EM-380 80 MHz FT NMR spectrometer using TMS as internal standard.

Substituted aryloxyphosphorodichloridates and cyclohexylphosphonic dichloride were prepared according to the literature procedures[6,7]. 2-Amino-3-hydroxypyridine of Aldrich (USA) grade was used as such.

2,3-Dihydro-2-phenoxy-1,3,2-oxazaphospholo-[4,5-b]pyridine-2-oxide (**1a**)

Phenoxyphosphorodichloridate (4.22 g, 0.02 mol) in dry toluene (20 ml) was added dropwise during 30 min to a solution of 2-amino-3-hydroxypyridine (2.2 g, 0.02 mol), dry pyridine (10 ml) and triethylamine (4.05 g, 0.04 mol) in dry toluene (40 ml) at 50-60° with stirring. The temperature of the reaction mixture was raised slowly till reflux which was maintained for 5½ hr. Thereafter, the precipitated solid was filtered hot and washed successively with water to eliminate triethylamine hydrochloride and hot methanol to remove the starting material, if any. The compound **1a** (3.5 g, 71%) remained as a colourless pluffy solid, m.p. 234° (d). This typical procedure was used for the preparation of other compounds (**1b-f**).

The authors are thankful to Dr Kurt Loening, Nomenclature Director, Chemical Abstract Service, for suggesting the names for these compounds, and to Dr M S Raju for PMR spectra.

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Synthesis of 2-(N-Substitutedaryl-carbamoyl)-quinazolin-4(3*H*)-ones & Benzofurans as Potential Anthelmintics

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The 2-[N(3′-substituted-aminomethyl-4′-hydroxyphenyl)carbamoyl]quinazolin-4(3*H*)-ones (**7-17**) and 2-[N-(3′-substituted-aminomethyl-4′-hydroxyphenyl)carbamoyl]benzofurans (**20-30**) have been synthesised and tested for their anthelmintic activity against *Brugia pahangi* and *Hymenolepis nana* in jirds and rats, respectively. Compound **29** is found to be the most active member of the series showing 65% clearance of *H. nana* infection at a dose of 250 mg/kg for 3 days.

Although a number of compounds exhibit microfilaricidal activity, very little progress has been made in finding effective macrofilaricides[1]. Some antimonials and arsenicals do possess high activity against adult filarial worms but are highly toxic to the host and show serious side effects[2]. The macrofilaricidal activity exhibited by amodiaquin, though weak[3] prompted us to synthesize some of its structural analogs bearing a quinazolone or benzofuran nucleus in place of quinoline moiety. The present note describes the synthesis of 2-[N-(3′-substituted-aminomethyl-4′-hydroxyphenyl)carbamoyl]quinazolin-4(3*H*)-ones (**7-17**) and 2-[N-(3′-substituted-aminomethyl-4′-hydroxyphenyl)carbamoyl]benzofurans (**20-30**). The antifilarial and cestodicidal activities of these compounds are also reported.

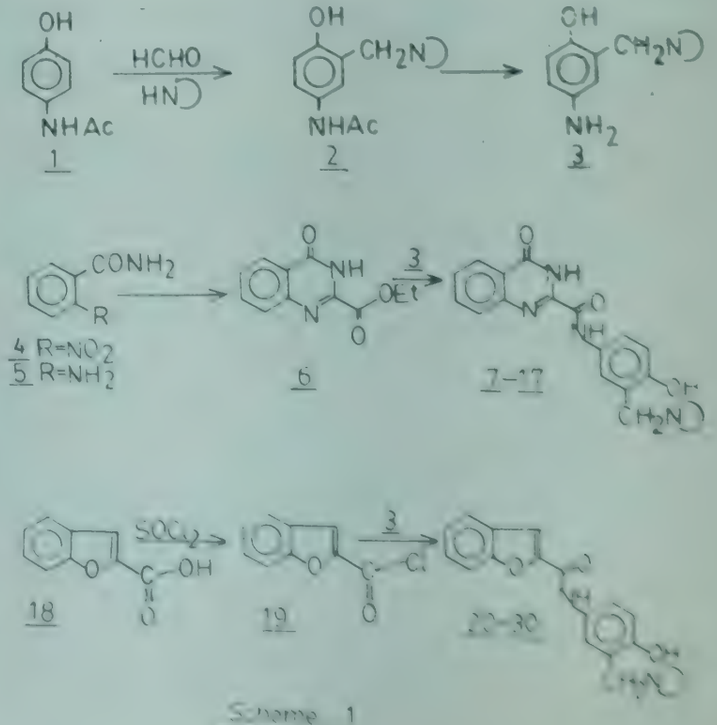
Mannich reaction of 4-acetamidophenol (**1**) with formaldehyde and various amines yielded 2-substituted-aminomethyl-4-acetamidophenol (**2**) which on hydrolysis with 25% HCl afforded the corresponding amino compound (**3**)[4]. Condensation of the anthranilamide (**5**), obtained by reduction of *o*-nitrobenzamide (**4**) with diethyl oxalate yielded 2-carbethoxyquinazolone (**6**)[5]. Reaction of **3** with **6** yielded 2-[N-3′-substituted-aminomethyl-4′-hydroxyphenyl)carbamoyl]quinazolin-4(3*H*)-ones (**7-17**; Table 1).

Benzofuran-2-carbonyl chlorides (**19**), obtained by treating benzofuran-2-carboxylic acid (**18**)[6] with thionyl chloride, was reacted with **3** in dry DMF to afford 2-[N-(3′-substituted-aminomethyl-4′-hydroxy phenyl)carbamoyl]benzofurans (**20-30**; Table 1) (Scheme 1).

Table 1—Physical Data of the Compounds **7-17** and **20-30**

Compd	–N	m.p. °C	Mol. formula*
7	Diethylamino	113-14	$C_{20}H_{22}N_4O_3$
8	1-Pyrrolidinyl	130	$C_{20}H_{20}N_4O_3$
9	Piperidino	180-81	$C_{21}H_{22}N_4O_3$
10	4-Methyl-1-piperazinyl	170	$C_{21}H_{23}N_5O_3$
11	4-Phenyl-1-piperazinyl	186-87	$C_{26}H_{25}N_5O_3$
12	4-(*p*-Chlorophenyl)-1-piperazinyl	152-53	$C_{26}H_{24}ClN_5O_3$
13	2-Methyl-1-piperidinyl	165	$C_{22}H_{24}N_4O_3$
14	4-Phenylpiperidino	147-48	$C_{27}H_{26}N_4O_3$
15	4-Hydroxy-4-phenyl-piperidino	133-34	$C_{27}H_{26}N_4O_4$
16	Homopiperidino	192-93	$C_{22}H_{24}N_4O_3$
17	Morpholinyl	157-58	$C_{20}H_{20}N_4O_4$
20	Diethylamino	131	$C_{20}H_{22}N_2O_3$
21	1-Pyrrolidinyl	114	$C_{20}H_{20}N_2O_3$
22	Homopiperidino	168	$C_{22}H_{24}N_2O_3$
23	Morpholinyl	84-85	$C_{20}H_{20}N_2O_4$
24	Piperidino	112-13	$C_{21}H_{22}N_2O_3$
25	2-Methylpiperidino	172	$C_{22}H_{24}N_2O_3$
26	4-Phenylpiperidino	156-57	$C_{27}H_{26}N_2O_3$
27	4-Hydroxy-4-phenyl-piperidino	162-63	$C_{27}H_{26}N_2O_4$
28	4-Methyl-1-piperazinyl	179	$C_{21}H_{23}N_3O_3$
29	4-(*p*-Chlorophenyl)-1-piperazinyl	145	$C_{26}H_{24}ClN_3O_3$
30	4-Phenyl-1-piperazinyl	198	$C_{26}H_{25}N_3O_3$

*The elementary analysis (C, H and N) are within the range of ±0.5%.



Scheme 1

Anthelmintic activity

The compounds were tested for their antifilarial activity against *Brugia pahangi* in jirds (*Meriones unguiculatus*). Each of jirds was infected by the i.p. implantation of adult *B. pahangi* using the technique of Suswillo and Denham[7]. The test compounds were injected sub-cutaneously suspended in 0.5% Tween 80 on five successive days at 100 mg/kg giving a total dose of 500 mg/kg[8]. None of the compounds showed activity in the tests.

The compounds were also screened for their cestodicidal activity against *Hymenolepsis nana* infection in rats using the technique of Steward[9] with slight modifications. The compounds were given orally at doses of 500, 400 and 250 mg/kg using 3 rats per experimental group. Yomesan was used as the standard drug in all the control experiments and it cleared 100% of the tapeworms without scolices at a single oral dose of 50 mg/kg.

In a preliminary screening of anticestode activity against *Hymenolepis nana* it was revealed that compounds **12** and **29-30** given at a dose of 250 mg/kg for 3 days induce 60-65% worm expulsion in rats while compounds **9-11**, **14**, **15**, **22**, **24-26** and **28** also exhibit activity showing inhibition of worm load from 27-55% at a dose of 250 mg/kg for 3 days. The rest of the compounds were either found inactive or showed insignificant activity at 500 and 400 mg/kg dose levels.

Structures of all the compounds were checked by their IR and PMR spectra recorded respectively on Perkin-Elmer 157 infracord (ν_{max} in cm^{-1}) and Perkin-Elmer R-32 instrument (chemical shifts in δ scale downfield from TMS as standard). The mass spectra were taken on a Jeol-JMS-D-300 spectrometer.

2-[*N*-(4′-*Hydroxy*-3′-*pyrrolidinomethylphenyl*)-*carbamoyl*]*quinazolin*-4(3*H*)-*one* (**8**)

A mixture of 2-(1-pyrrolidinylmethyl)-4-aminophenol (1.92 g, 0.01 mol) and 2-carbethoxyquinazolone (2.18 g, 0.01 mol) was heated to gentle boiling for 1 hr. On cooling, a semisolid separated out which was shaken with ethanol. The solid thus obtained was crystallised from benzene, yield 2.5 g (69%), m.p. 130°; IR(KBr): 1730 (CONH); PMR(DMSO-d_6): 1.62-1.89 (*m*, 4H, N$-CH_2CH_2CH_2$), 2.40-2.77 [*m*, 4H, $N(CH_2)_2$], 3.52 (*s*, 2H, Ar$-CH_2N$), 6.00 (*hump*, 2H, NH), 7.00-7.52 (*m*, 8H, Ar$-H$ and OH); MS: *m/z* 364 (M^+) (Found: C, 65.5; H, 5.0; N, 15.0. $C_{20}H_{20}N_4O_3$ requires C, 65.9; H, 5.5; N, 15.4%).

In a similar way compounds **7** and **9-17** (Table 1) were prepared.

2-[*N*-4′-*Hydroxy*-3′-(4-*phenyl*-1-*piperazinyl*-*methyl*)*phenylcarbamoyl*]*benzofuran* (**30**)

A mixture of **19** (1.80 g, 0.01 mol) and 2-(1-phenyl-4-piperazinylmethyl)-4-aminophenol (2.83 g, 0.01 mol) in dry DMF was refluxed for 10 hr. The reaction mixture was poured into water, the separated solid filtered and crystallized from benzene, yield 3 g (71%), m.p. 198°; IR(KBr): 1640 (CONH), 3200 (NH); PMR($CDCl_3$): 2.63-3.00 [*m*, 4H, $CH_2N(CH_2)_2$], 3.15-3.43 [*m*, 4H, Ar$-N(CH_2)_2$], 3.63 (*s*, 2H, Ar$-CH_2N$), 6.60-7.30 (*m*, 15H, Ar$-H$, CONH and OH); MS: *m/z* 427 (M^+) (Found: C, 72.7; H, 5.4; N, 9.4. $C_{26}H_{25}N_3O_3$ requires C, 73.1; H, 5.9; N, 9.8%).

Other compounds **20-29** were prepared in a similar manner and their characterization data are given in Table 1.

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Fused Thiazoles: Synthesis & Antifungal Activity of 2-Arylidenethiazolo[3′,2′:1,2]imidazo[5,4-*b*]pyridin-3(2*H*)-ones, 2-Arylidenethiazolo-[3,2-*a*]benzimidazol-3(2*H*)-ones & 6-Arylidenethiazolo[3,2-*b*]-*s*-triazol-5(6*H*)-ones

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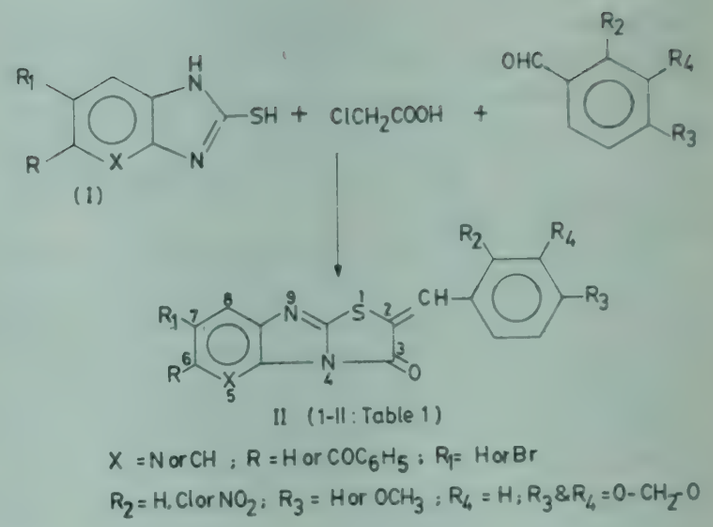
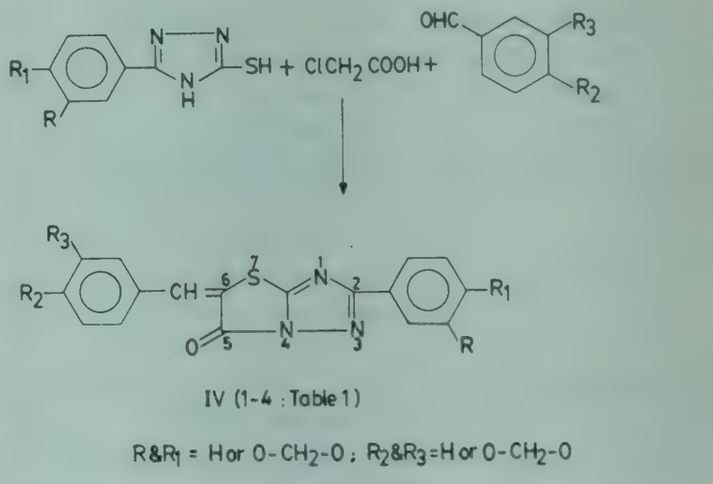
One-pot synthesis of the title compounds (II, IV) starting from 2-mercapto-1*H*-imidazo[4,5-*b*]pyridines (I; X = N), 2-mercapto-benzimidazoles (I; X = CH) or 5-aryl-3-mercapto-1,2,4-triazoles (III) is described. These compounds have been screened for their antifungal activities.

Thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones[1,2] are reported to exhibit antifungal and antibacterial activities and incorporation of arylidene moiety[3] into the heterocyclic residue leads to the compounds possessing antifungal activity. A survey of literature reveals that thiazoles fused to imidazo[4,5-*b*]pyridines and to *s*-triazoles carrying arylidene moiety at 2-position have not yet been prepared and explored for their biological activity. The earlier work from our laboratory[4] that fused *s*-triazoles possess a variety of biological actions, prompted us to synthesise thiazoles fused to pyrido/benzimidazole and *s*-triazole moieties and study their fungicidal properties.

In literature[1,5] the preparation of 2-arylidene-thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones has been reported to involve three steps starting from 2-mercapto-1*H*-benzimidazole. In this note we wish to report a convenient one-pot synthesis of 2 arylidenethiazolo[3′,2′:1,2]imidazo[5,4 *b*]pyridin-3(2*H*)-ones (II_{1-4}), 2-arylidene thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (II_{5-11}) and 6-arylidene-2-arylthiazol[3,2-*b*]-*s*-triazol 5(6*H*)-ones (IV_{1-4}) by reacting 2-mercapto-1H-imidazo[4,5-*b*]pyridines (I, X = N), 2-mercapto-benzimidazoles (I, X = CH) and 5-aryl-3-mercapto-1,2,4-triazoles (III) respectively with chloroacetic acid and aromatic aldehydes in the presence of acetic anhydride and sodium acetate (Scheme 1). The 2-mercapto-6-substituted-1*H*-imidazo[4,5-*b*]pyridines[6], 2-mercapto 5,6-disubstituted-1*H*-benzimidazoles[7] and 5-aryl-3-mercapto-1,2,4-triazoles[8] in turn were





Scheme 1

prepared following the literature methods. The structures II and IV for the products in preference to their alternate possible isomers were based on literature evidences[9,10].

The structural assignments of II and IV were based on their elemental analyses and IR and mass spectral data. Homogeneity of all the compounds was checked by TLC. The characterisation of II and IV and their fungicidal activities are given in Table 1.

Antifungal activity

Compounds II were tested against the fungi *Aspergillus flavus*, *Penicillium tardum*, *Fusarium oxysporium* and *Alternaria alternata* by Disc method[11] at 10 mg/ml concentration using Nystatin as standard (the inhibition zones are expressed in millimeters). It is observed from Table 1 that none of the compounds exhibits promising antifungal activity to warrant

Table 1—Characterization and Antifungal Activity Data of 2-Arylidenethiazolo[3′,2′:1,2]imidazo[5,4-*b*]pyridin-3(2*H*)-ones (II_{1-4}) 2-Arylidenethiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones (II_{5-11}) and 6-Arylidenethiazolo[3,2-*b*]-*s*-triazol-5(6*H*)-ones (IV_{1-4})

Compd	X	R	R_1	R_2	R_3	R_4	m.p. °C	Yield (%)	Mol. formula*	Antifungal activity (in mm) against		
										A. flavus	P. tardum	F. oxysporium	A. alternata
	N	H	H	H	H	H	276	70	$C_{15}H_9N_3OS$	12	11	13	9
II_2	N	H	Br	H	H	H	305	68	$C_{15}H_8N_3OSBr$	8	14	16	11
II_3	N	H	H	H	O–CH_2–O		300	66	$C_{16}H_9N_3O_3S$	10	15	11	8
II_4	N	H	Br	H	O–CH_2–O		305	64	$C_{16}H_8N_3O_3Br$	9	15	16	12
II_5	CH	H	H	H	H	H	226 (226)[4]	70	$C_{16}H_9N_2OS$	9	10	14	9
II_6	CH	H	H	Cl	H	H	235	70	$C_{16}H_9N_2OSCl$	12	13	8	8
II_7	CH	H	H	NO_2	H	H	240	68	$C_{16}H_9N_3O_3S$	11	14	13	10
II_8	CH	H	H	H	OCH_3	H	205	66	$C_{17}H_{12}N_2O_2S$	6	12	10	9
II_9	CH	H	H	H	O–CH_2–O		248	65	$C_{17}H_{10}N_2O_3S$	13	20	11	8
II_{10}	CH	COC_6H_5	H	H	H	H	295	66	$C_{23}H_{14}N_2O_2S$	5	8	6	4
II_{11}	CH	COC_6H_5	H	H	O–CH_2–O		305	64	$C_{24}H_{14}N_2O_4S$	7	12	8	7
IV_1	—	H	H	H	H	—	239	75	$C_{17}H_{11}N_3OS$	—	—	—	—
IV_2	—	O–CH_2–O		H	H	—	242	70	$C_{18}H_{11}N_3O_3S$	—	—	—	—
IV_3	—	H	H	O–CH_2–O		—	249	70	$C_{18}H_{11}N_3O_3S$	—	—	—	—
IV_4	—	O–CH_2–O		O–CH_2–O		—	253	70	$C_{19}H_{11}N_3O_5S$	—	—	—	—
Nystatin										15	16	18	14

*Satisfactory C, H and N analyses were obtained for all the compounds

further investigation. However, the activity of II_9 against *Penicillium tardum* is comparable to that of Nystatin. Compounds of the type IV did not show any antifungal activity.

Melting points were taken on a Boetus heating table melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on Perkin-Elmer 221 and 283B spectrophotometers (ν_{max} cm^{-1}) and mass spectra on a Hitachi RMU 6L mass spectrometer at 70 eV.

2-(3,4-*Methylenedioxybenzylidene*)*thiazolo*-[3,2-*a*]*benzimidazol*-3(2*H*)-*one* (II_9)

A mixture of 2-mercapto-1*H*-benzimidazole (1.5 g, 0.01 mol), chloroacetic acid (1.43 g, 0.015 mol), fused sodium acetate (2 g) and 3,4-methylenedioxybenzaldehyde (1.5 g, 0.01 mol) in acetic anhydride (15 ml) and glacial acetic acid (20 ml) was refluxed for 2 hr and cooled. The product obtained after dilution was filtered and recrystallised from acetic acid to give II_9, yield 2.1 g (65%), m.p. 248°; IR: 1720 (C=O), 2900 (methylenedioxy CH_2); MS: *m/z* 322 (M^+; 100%), 294 ($M^+ - CO$; 21%), 236 ($M^+ - CO - CNS$; 10%), 133 ($M^+ - CO - CNS - C_8H_7$; 30%) and lower mass peaks.

Compounds II_{1-8} and $II_{10,11}$ listed in Table 1 were prepared in a similar manner by the reaction of I with chloroacetic acid and appropriate aldehydes.

6-*Benzylidene*-2-(3,4-*methylenedioxyphenyl*)-*thiazolo*[3,2-*b*]-*s*-*triazol*-5(6*H*)-*one* (IV_2)

A mixture of 3-mercapto-5-(3,4-methylenedioxyphenyl)-1,2,4-triazole (4.42 g, 0.02 mol), chloroacetic acid (2.85 g, 0.03 mol), fused sodium acetate (4 g) and benzaldehyde (2.12 g, 0.02 mol) in acetic anhydride (30 ml) and gl. acetic acid (40 ml) was refluxed for 2 hr, cooled and diluted with water. The precipitate was filtered and recrystallised from aq. dioxane to give IV_2, yield 4.9 g (70%), m.p. 242°; IR: 1720 (C=O), 2920 (methylenedioxy CH_2); MS: *m/z* 349 (M^+; 100%), 321 ($M^+ - CO$; 10%), 174 ($M^+ - CO - C_8H_5NO_2$; 18%); 147 ($M^+ - CO - C_9H_6N_2S$; 40%) and lower mass peaks.

Compounds $IV_{1,3,4}$ listed in Table 1 were prepared in a similar way by the reaction of III with chloroacetic acid and corresponding aldehydes.

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Synthesis & Pharmacological Properties of Some 4-(2′-Benzo[*b*]furanyl)coumarins

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4-(2′-Benzo[b]furanyl) coumarins (III) have been prepared by reacting salicylaldehydes with 4-bromomethylcoumarins (I) via two routes, and screened for their antiinflammatory, analgesic and hypotensive activities.

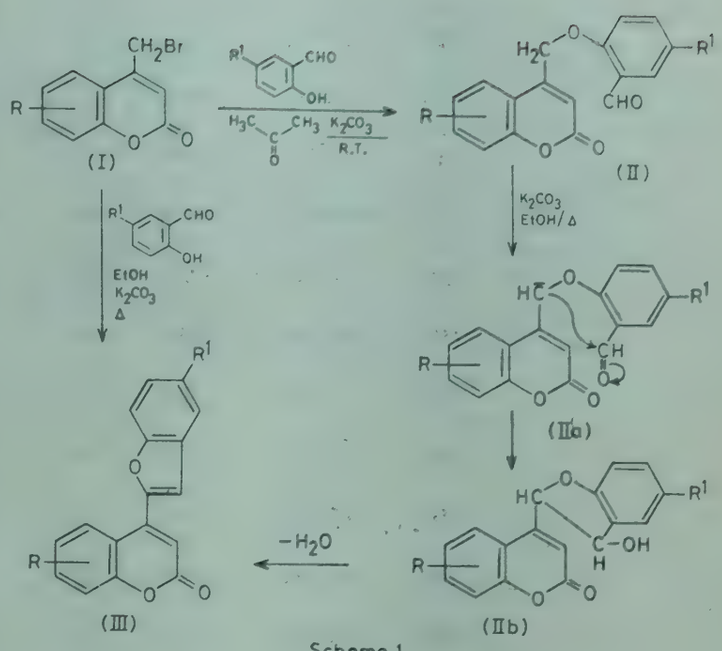
Certain pyridyl- and furyl-coumarins have been found to be CNS depressant[1] and bacteriostatic[2] agents respectively. Further, some 2-heteroarylbenzofurans are reported as CNS agents[3] and inflammation inhibitors[4]. In continuation of our earlier work on heteroarylcoumarins[5] we have now synthesized some 4-(2′-benzo[*b*]furanyl)coumarins (III) and evaluated their biological activities.

The 4-bromomethylcoumarins (I)[6-8] were converted into III by two routes. In the first route, a facile conversion of I into III occurred when the former were refluxed with equimolar quantities of appropriately substituted salicylaldehydes in ethanol in the presence of potassium carbonate. In the second route, the intermediate aryloxyaldehydes (II) were synthesised by the base-catalysed nucleophilic substitution at the methylene carbon of I at room temperature, and converted into III in high yields under similar conditions as employed in the first route (Scheme 1).

The formation of III involves an intramolecular carbanion addition across the carbonyl group in IIa followed by dehydration of the resultant IIb. The structural assignments of III were based on their elemental analyses and UV, IR and PMR spectral data. Their characterization data are given in Table 1.

Biological screening results

The acute toxicity studies of compounds III in albino rats indicated that they were well tolerated upto a dose level of 800 mg/kg (i.p.). The antiinflammatory activity of III was determined by the method of Winter *et al*[9]. and the results showed that halogenation in both the heterocyclic rings abolished the activity while alkylation enhanced the same. Amongst the



Scheme 1

compounds tested, IIIa, IIId and IIIf showed 43%, 38% and 65% inhibition respectively against the carageenan-induced inflammation in rat paw. In the tail clip test[10] for analgesic activity only IIIa showed 33% analgesic activity while others were less effective. In the hypotensive activity test, compound IIIa showed the reduction of systemic blood pressure in rats by 50 mm but there was no significant change in the ECG pattern.

Melting points were determined in open capillaries and are uncorrected. UV spectra were recorded on a Carl-Zeiss double beam spectrometer using 1 cm quartz cells (λ_{max} in nm), IR spectra in nujol or KBr on a Perkin-Elmer spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ at 60 MH on a Varian A-60 instrument using TMS as internal standard (chemical shifts in δ, ppm).

6-Methyl-4(o-formylphenoxymethyl)coumarin (IIa)

A mixture of anhydr. potassium carbonate, (1.8 g), salicylaldehyde (0.004 mol) and dry acetone (30 ml) was stirred at room temperature for 30 min. To this was added 6-methyl-4-bromomethylcoumarin (0.004 mol) and the stirring continued for 24 hr. The reaction mixture was then concentrated and diluted with water (100 ml). The separated solid was filtered and washed with dilute ethanol (100 ml) and the residue recrystallised from 1,2-dichloroethane to give IIa as silky needles, m.p. 252°, yield 1 g (80%) (Found: C, 73.3; H, 4.7. $C_{18}H_{13}O_4$ requires C, 73.5; H, 4.8%); IR: 1700 (C=O), 1200 and 1250 (C–O–C); PMR (TFA): 2.1

Table 1 – Characterization Data of 4-(2'-Benzo[*b*]furanyl)coumarins (III)

Compd	R	R^1	Yield (%)	m.p. °C	Mol. formula	Found (Calc %)	
						C	H
IIIa	6-CH_3	–H	84	155	$C_{18}H_{12}O_3$	78.1 (78.3	4.2 4.3)
IIIb	6-CH_3	–CH_3	75	158	$C_{19}H_{14}O_3$	78.4 (78.6	4.6 4.8)
IIIc	6-CH_3	–Br	78	206	$C_{18}H_{11}O_3Br$	60.7 (60.8	2.8 3.1)
IIId	6-CH_3	–Cl	80	199	$C_{18}H_{11}O_3Cl$	69.4 (69.5	3.3 3.5)
IIIe	7-CH_3	–H	83	145	$C_{18}H_{12}O_3$	78.1 (78.3	4.2 4.3)
IIIf	7-CH_3	–CH_3	80	180	$C_{19}H_{14}O_3$	78.5 (78.6	4.7 4.8)
IIIg	7-CH_3	–Br	73	205	$C_{18}H_{11}O_3Br$	60.7 (60.8	2.9 3.1)
IIIh	7-CH_3	–Cl	76	200	$C_{18}H_{11}O_3Cl$	69.4 (69.5	3.4 3.5)
IIIi	6-OCH_3	–H	71	160	$C_{18}H_{12}O_4$	78.8 (74.0	4.0 4.1)
IIIj	6-OCH_3	–Br	68	222	$C_{18}H_{11}O_4Br$	58.0 (58.2	2.8 3.0)
IIIk	6-OCH_3	–Cl	72	212	$C_{18}H_{11}O_4Cl$	66.0 (66.1	3.1 3.3)
IIIl	7-OCH_3	–H	80	147	$C_{18}H_{12}O_4$	73.7 (74.0	4.0 4.1)
IIIm	7-OCH_3	–CH_3	78	155	$C_{19}H_{14}O_4$	74.3 (74.5	4.3 4.6)
IIIn	7-OCH_3	–Br	69	193	$C_{18}H_{11}O_4Br$	58.2 (58.2	2.7 3.0)
IIIo	7-OCH_3	–Cl	73	190	$C_{18}H_{11}O_4Cl$	65.9 (66.1	3.1 3.3)
IIIp	6-Cl	–H	79	150	$C_{17}H_9O_3Cl$	68.6 (68.9	2.9 3.0)
IIIq	6-Cl	–CH_3	75	145	$C_{18}H_{11}O_3Cl$	69.4 (69.5	3.3 3.5)
IIIr	6-Cl	–Br	73	205	$C_{17}H_8O_3ClBr$	54.1 (54.3	2.0 2.1)
IIIs	6-Cl	–Cl	74	206	$C_{17}H_8O_3Cl_2$	61.4 (61.6	2.3 2.4)
IIIt	7-Cl	–H	78	170	$C_{17}H_9O_3Cl$	68.6 (68.8	2.9 3.0)
IIIu	7-Cl	–CH_3	70	180	$C_{18}H_{11}O_3Cl$	69.3 (69.5	3.3 3.5)
IIIv	7-Cl	–Br	72	215	$C_{17}H_8O_3BrCl$	54.1 (54.3	1.9 2.1)
IIIw	7-Cl	–Cl	73	216	$C_{17}H_8O_3Cl_2$	61.4 (61.6	2.3 2.4)
IIIx	–H	–H	78	162	$C_{17}H_{10}O_3$	77.7 (77.8	3.7 3.8)

Compounds IIIj, IIIk, IIIn were recrystallised from benzene while IIIp was recrystallised from pet. ether (60-80°). All the remaining compounds were recrystallised from ethanol.

(3H, *s*, coumarin C_6-CH_3), 5.2 (2H, *d*, $-CH_2-O$), 6.6 (1H, *s*, coumarin 3-H), 6.8-7.6 (7H, *m*, Ar-*H*), 9.0 (1H, *s*, CHO).

Other members of the Series II were prepared in a similar way from appropriate salicylaldehydes and 4-bromomethylcoumarins.

4-(2'-Benzo[b]furanyl)coumarins (III): General method

To a solution of I (0.005 mol) and the appropriate salicylaldehyde (0.005 mol) in abs. ethanol (50 ml) was added potassium carbonate (1.8 g) and the mixture refluxed on a water-bath for 5 hr and filtered. The filtrate was concentrated, cooled to room temperature

and poured into ice-cold water (100 ml). The separated solid was washed with water and recrystallised from a suitable solvent to give III (Table 1). IIIa – UV: 335 (log ε 4.26); IR 1700 (C=O); PMR: 2.47 (3H, *s*, coumarin C_6-CH_3), 6.8 (1H, *s*, coumarin 3-H), 7.2-7.9 (8H, *m*, Ar–*H*); MS: *m/z* 276 (M^+, 100%).

The authors are thankful to Prof. V V Badiger for encouragement and to Shri V A Desai for elemental analyses.

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BOOK REVIEWS

Medicinal Chemistry Research in India by Harkishan Singh, A S Chawla and V K Kapoor (National Information Centre for Drugs & Pharmaceuticals, CDRI, Lucknow), 1985, pp. 184. Price Rs 150 ($ 35.00).

The book is a comprehensive compendium of published information in this area from Indian laboratories. The authors deserve congratulations for having summarised succinctly and successfully in 20 chapters comprising a total of 166 pages, an enormous volume of work spanning three to four decades (with emphasis on the last decade) and appearing in diverse journals. Apart from convering conventional areas ranging from anthelmintic agents (Chapter 2) to antifertility agents (Chapter 16), the authors have thoughtfully included subjects, such as QSAR (Chapter 18), prostaglandins (Chapter 19) and peptides (Chapter 20). The dispensation of information is generally accurate, although a reference to the activity of coleonol (forskolin) against glautoma is surprisingly lacking. Also, it may be mentioned that satranidazole and nonaperone maleate (p. 2) have been granted registration. This information, perhaps, may have become available only after the preparation of the manuscript.

Medicinal chemistry research is an indispensable part of new drug development, which, however, encompasses a large number of other activities, calling for a multidisciplinary effort, preferably under one roof. The reviewer wonders whether a short account of the nature of the new drug development process could not have been usefully added to the introduction of the book. This would have helped the non-expert reader assess the Indian work in its correct perspective. Otherwise, he is likely to commit the mistake of considering all medicinal chemistry research reported in this monograph as being directed towards new drug research. The fact is that atleast a part of this work is being carried out in institutions which do not have this objectives; nor will the work result in a new drug.

The monograph is produced well and is mostly free of errors. The provision of subject and author indices makes referencing easier, although the reviewer checking a few times, found some mistakes in the case of coleonol. Thus, there are no references to this on pages 1 and 145, the latter being probably a mistake for p. 144. The National Information Centre for Drugs and Pharmaceuticals of CDRI, Lucknow, deserves our appreciation for having brought out this well-designed and attractive publication. The price of almost one rupee per page, small by international standards, is affordable by our libraries and by the more affluent Indian Academics!

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